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| (54) Title: 6-SUBSTITUTED BIARYL PURINE DERIVATIVES AS POTENT CYCLIN/CDK INHIBITORS AND ANTIPROLIFERATIVE AGENTS (57) Abstract The present invention is directed to 2,6,9-trisubstituted purines cellular proliferation. Processes of preparing such compounds are also disclosed. | | |

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6-SUBSTITUTED BIARYL PURINE DERIVATIVES AS POTENT CYCLIN/CDK INHIBITORS AND ANTIPROLIFERATIVE AGENTS

This application claims benefit of U.S. Provisional Patent Application
5 Serial No. 60/124.829, filed March 17, 1999.

FIELD OF THE INVENTION

The present invention relates to compounds that are shown to be potent
10 cyclin/cyclin dependent kinase (cdk) inhibitors. Compounds with these properties are
shown to be potent inhibitors of cell growth and proliferation. Such compounds can
be used to treat the following conditions: rheumatoid arthritis, lupus, type 1 diabetes,
multiple sclerosis, cancer, restenosis, gout and other proliferative diseases involving
abnormal cellular proliferation. Compounds of the present invention which are biaryl
15 substituted purine derivatives are shown to be potent antiproliferative agents against a
number of human transformed cell lines, and also inhibitors of human cyclin/cdk
kinase complexes.

BACKGROUND OF THE INVENTION

20

Cellular Proliferation and Cancer.

The disruption of external or internal regulation of cellular growth can
lead to uncontrolled proliferation and in cancer, tumor formation. This loss of control
can occur at many levels and, indeed, does occur at multiple levels in most tumors.

25 Further, although tumor cells can no longer control their own proliferation, they still
must use the same basic cellular machinery employed by normal cells to drive their
growth and replication.

Cyclin Dependent Kinases and Cell Cycle Regulation.

30 Progression of the normal cell cycle from the G1 to S phase, and from
the G2 phase to M phase is dependent on cdks (Sherr, C.J., Science 274:1672-1677
(1996)). Like other kinases, cdks regulate molecular events in the cell by facilitating
the transfer of the terminal phosphate of adenosine triphosphate (ATP) to a substrate

protein. Isolated cdks require association with a second subunit, called cyclins (Desai et al., Mol. Cell. Biol., 15:345-350 (1995)). Cyclins cause conformational changes at the cdk active site, allowing ATP access and interaction with the substrate protein. The balance between its rates of synthesis and degradation controls the level of each cyclin at any point in the cycle (Elledge, S.J., et al., Biochim. Biophys. Acta, 1377:M61-M70 (1998)). The influences of cyclin/cdk activity on the cell cycle and cellular transformation are summarized in Table 1.

Abnormal Cyclin/cdk Activity in Cancer.

10 In a normal cell, interlocking pathways respond to the cell's external environment and internal checkpoints monitor conditions within the cell to control the activity of cyclin/cdk complexes. A reasonable hypothesis is that the disruption of normal control of cyclin/cdk activity may result in uncontrolled proliferation. This hypothesis appears to hold in a number of tumor types in which cyclins are expressed
15 at elevated levels (Table 1). Mutations in the genes encoding negative regulators (proteins) of cyclin/cdk activity are also found in tumors (Larsen, C.-J., Prog. Cell Cycle Res., 3:109-124 (1997)); (Kamb, A., Trends in Genetics, 11:136-140 (1995)). Members of the Cip family of cdk inhibitors form a ternary complex with the cyclin/cdk and require binding to cyclinA, cyclinE, or cyclinD (Hall, M., et al.,
20 Oncogene, 11:1581-1588 (1995)). In contrast, Ink family members form a binary complex with cdk4 or cdk6 and prevent binding to cyclinD (Parry, D.; et al., EMBO J., 14:503-511 (1995)).

Table 1. Associations Among Cyclins and Cancers

| Cyclin | Cell Cycle Role | Associated cdk | Cancer |
|--------|-----------------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A | S, G2 to M | cdk1, cdk2 | hepatocellular carcinoma (Wang, J.; et al., <u>Oncogene</u> , 8:1653-1656-(1992)) |
| B1/B2 | G2 to M | cdk1 | none yet defined |
| D1 | G1 | cdk4, cdk6 | parathyroid adenoma (Motokura, T., et al., <u>Nature</u> , 350:512-515 (1991)) centrocytic B cell lymphoma (Withers, D.A., et al., <u>Mol. Cell. Biol.</u> , 11:4846-4853 (1991)) esophageal carcinoma (Jiang, W., et al., <u>Cancer Res.</u> , 52:2980-2983 (1992)) breast cancer (Dickson, C., et al., <u>Cancer Lett.</u> , 90:43-50 (1995)) squamous cell carcinoma (Bartkova, J., et al., <u>Cancer Res.</u> , 55:949-956 (1995)) hepatocellular carcinoma (Nishida, N., et al., <u>Cancer Res.</u> , 54:3107-3110 (1994)) |
| D2 | G1 | cdk4, cdk6 | colorectal carcinoma (Leach, F.S., et al., <u>Cancer Res.</u> , 53:1986-1989 (1993)) breast cancer (Keytomarsi, K., et al., <u>Cancer Res.</u> , 54:380-385 (1994)) |
| E | G1 to S | cdk2 | gastric carcinoma (Akama, Y.; et al., <u>Jap. J. Cancer Res.</u> , 86:617-621 (1995)) colorectal carcinoma (Kitihara, K.; et al., <u>Int. J. Cancer</u> , 62:25-28 (1995)) |

5 Inhibitors of Cyclin/cdk Complexes as Potential Anticancer Agents.

Tumors with elevated cyclin/cdk activity, whether from the over expression of cyclins or the loss of an endogenous cdk inhibitor, are prime targets for potential therapies based on small molecule cyclin/cdk inhibitors. In fact, several small molecule inhibitors of cyclin/cdks are reported (Meijer, L., et al., "Progress in
 10 Cell Cycle Research," Plenum Press: New York, 351-363 (1995)) and appear to bind at the ATP site of the kinase. Some information is known about small molecule inhibitors of other kinases, such as PKC (serine kinase) (Murray, K.J. et al., "Ann. Rep. Med. Chem.," J. Bristol, Ed., Academic Press, Inc.: New York, Chapter 26 (1994)) and tyrosine kinases (Fantl, W.J., et al., Ann. Rev. Biochem., 62:453 (1993);
 15 Burke, T.R., Drugs of the Future, 17:119-1131 (1992); Dobrusin, E.M. et al., "Ann.

Rep. Med. Chem." J. Bristol, Ed., Academic Press, Inc.; New York, Chapter 18 (1992); Spence, P., Curr. Opin. Ther. Patents, 3:3 (1993)). A number of known inhibitors were obtained from commercial sources or were synthesized by literature procedures.

5

Purine Compounds as Cyclin/cdk Inhibitors.

There are several reports of 2,6-diamino substituted purine derivatives as cyclin/cdk inhibitors and as inhibitors of cellular proliferation. Among those are reports by U.S. Patent No. 5,583,137 to Coe, et al., olomoucine (Vesely, J., et al., Eur. J. Biochem., 224:771-786 (1994)), roscovitine (Meijer, L., Eur. J. Biochem., 243:527-536 (1997)), WO 97/16452 to Zimmerman, Imbach, P., et al., Bioorg. Med. Chem. Lett., 9:91-96 (1999), Norman, T.C., et al., J. Amer. Chem. Soc., 118:7430-7431 (1996), Gray, N.S., et al., Tetrahedron Lett., 38:1161-1164 (1997), Gray, N.S., et al., Science, 281:533-538 (1998), WO 98/05335 to Lum, et al., Schow, S.R., et al., Bioorg. Med. Chem. Lett., 7:2697-2702 (1997), US Patent No., 5,886,702 to Mackman, et al., Nugiel, D.A., et al., J. Org. Chem., 62:201-203 (1997), and Fiorini, M.T. et al., Tetrahedron Lett., 39:1827-1830 (1998). Many of these reported compounds are shown to inhibit cyclin/cdk complexes and have modest cellular proliferation inhibition properties.

20

The compounds of the present invention are shown to have far superior biological activities as cyclin/cdk complex inhibitors as well as inhibitors of cellular proliferation compared to those previously reported. In fact, the art (e.g., Fiorini, M.T. et al., Tetrahedron Lett., 39:1827-1830 (1998)) teaches away from compounds of this invention, claiming lack of cellular proliferation inhibition.

25

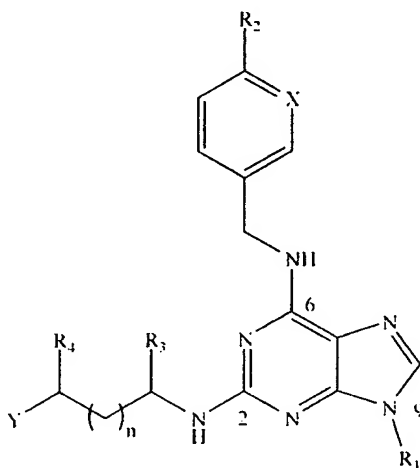
SUMMARY OF THE INVENTION

The compounds of the present invention are 2,6,9-trisubstituted purine derivatives which are inhibitors of cyclin/cdk complexes. The compounds of the current invention also are potent inhibitors of human cellular proliferation. As such, the compounds of the present invention constitute pharmaceutical compositions with a pharmaceutically acceptable carrier. Such compounds are useful in inhibiting cellular

30

proliferation in a mammal by administering to such mammal an effective amount of the compound.

In one embodiment, the compounds of the present invention are represented by the chemical structure found in Formula I



Formula I

wherein:

10 R_1 are the same or different and independently selected from:

H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

15 $X =$ N;
CH;

$R_2 =$ phenyl;
substituted phenyl, wherein the substituents (1-2 in number) are in any
20 position and are independently selected from R_1 , OR_1 , SR_1 , $S(O)R_1$,
 $S(O_2)R_1$, NHR_1 , NO_2 , $OC(O)CH_3$, $NHC(O)CH_3$, F, Cl, Br, CF_3 , $C(O)R_1$,
 $C(O)NHR_1$, phenyl, $C(O)NHCHR_1CH_2OH$;

1-naphthyl;
2-naphthyl;
25 heterocycles including:
2-pyridyl;
3-pyridyl;
4-pyridyl;
5-pyrimidyl;
30 thiophene-2-yl;
thiophene-3-yl;
2-furanyl;
3-furanyl;
2-benzofuranyl;

5 benzothiophene-2-yl;
 2-pyrrolyl;
 3-pyrrolyl;
 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
 3-isoquinolinyl;
 4-isoquinolinyl;
 10 substituted heterocycle, wherein the substituents (1-2 in number) are in any
 position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

R₃ are the same or different and independently selected from:

15 H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 20 above in R₂;

R₄= H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;

25 R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring;

n= 0-3;

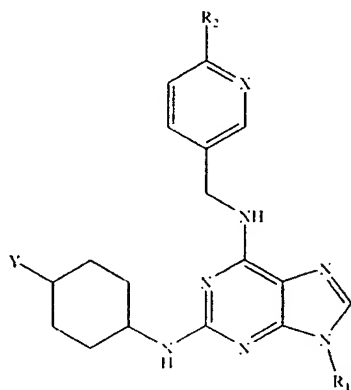
30 Y= H;
 OR₁;
 NHR₁;
 NHC(O)R₃;
 NHSO₂R₃;
 35 NHC(O)NHR₃;
 NHC(O)R₅;
 NHC(O)OR₆;

40 R₅= C₃-C₇-cycloalkyl;

45 R₆= C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 above in R₂;
 or a pharmaceutically acceptable salt thereof,

with the proviso that when $R_1 = \text{CH}(\text{CH}_3)_2$, and $R_2 = \text{Ph}$, and $X = \text{CH}$, then $R_3 \neq \text{H}$, and $n \neq 0$, and $R_4 \neq \text{H}$, and $Y \neq \text{OH}$.

- 5 Another aspect of the present invention is directed to a compound of the following formula:



Formula III

- 10 wherein:

R_1 are the same or different and independently selected from:

H;

C_1 - C_4 -straight chain alkyl;

- 15 C_3 - C_4 -branched chain alkyl;

$X =$ N;
CH;

- 20 $R_2 =$ phenyl;
substituted phenyl, wherein the substituents (1-2 in number) are in any position and independently selected from R_1 , OR_1 , SR_1 , $\text{S}(\text{O})\text{R}_1$, $\text{S}(\text{O}_2)\text{R}_1$, NHR_1 , NO_2 , $\text{OC}(\text{O})\text{CH}_3$, $\text{NHC}(\text{O})\text{CH}_3$, F, Cl, Br, CF_3 , $\text{C}(\text{O})\text{R}_1$, $\text{C}(\text{O})\text{NHR}_1$, phenyl, $\text{C}(\text{O})\text{NHCHR}_1\text{CH}_2\text{OH}$;

- 25 heterocycles including:

2-pyridyl;

3-pyridyl;

4-pyridyl;

5-pyrimidyl;

- 30 thiophene-2-yl;

thiophene-3-yl;

2-furanyl;

3-furanyl;

2-benzofuranyl;

- 35 benzothiophene-2-yl;

2-pyrrolyl;

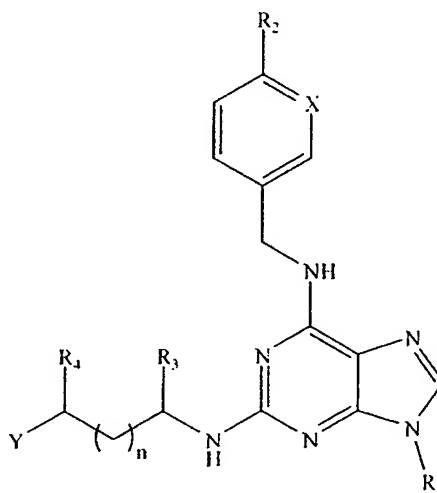
3-pyrrolyl;

2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
 3-isoquinolinyl;
 4-isoquinolinyl;
 substituted heterocycle, wherein the substituents (1-2 in number) are in any
 position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

Y= OR₁;
 NHR₁;
 NHC(O)R₁;
 NHSO₂R₁;
 NHC(O)NHR₁;
 NHC(O)OR₆; or a pharmaceutically acceptable salt thereof;

R₆ = C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 or a pharmaceutically acceptable salt thereof.

The present invention is also directed to a process for preparation of a
 purine derivative compound of the formula:



Formula XVIII

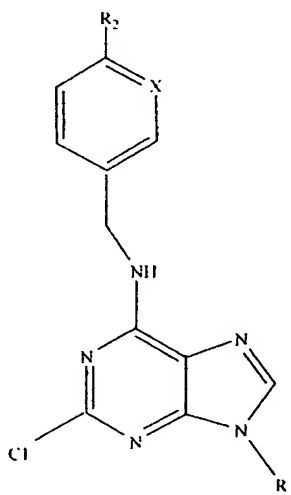
wherein:

R₁= H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;

- X= N:
CH:
- 5 R₂= phenyl;
substituted phenyl, wherein the substituents (1-2 in number) are in any
position and are independently selected from R₁, OR₁, SR₁, S(O)R₁,
S(O₂)R₁, NHR₁, NO₂, OC(O)CH₃, NHC(O)CH₃, F, Cl, Br, CF₃, C(O)R₁,
C(O)NHR₁, phenyl, C(O)NHCHR₁CH₂OH:
1-naphthyl;
10 2-naphthyl;
heterocycles including:
2-pyridyl;
3-pyridyl;
4-pyridyl;
15 5-pyrimidyl;
thiophene-2-yl;
thiophene-3-yl;
2-furanyl;
3-furanyl;
20 2-benzofuranyl;
benzothiophene-2-yl;
2-pyrrolyl;
3-pyrrolyl;
2-quinolinyl;
25 3-quinolinyl;
4-quinolinyl;
1-isoquinolinyl;
3-isoquinolinyl;
4-isoquinolinyl;
30 substituted heterocycle, wherein the substituents are in any position and are
selected from Br, Cl, F, R₁, C(O)CH₃;
- R₃= H;
C₁-C₄-straight chain alkyl;
35 C₃-C₄-branched chain alkyl;
C₂-C₄-alkenyl chain;
(CH₂)_nPh;
(CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
above in R₂;
40 R₄= H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;
- 45 R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring;
- n= 0-3;

- Y= H;
 OR₁;
 NHR₁;
 NHC(O)R₃;
 5 NHSO₂R₃;
 NHC(O)NHR₃;
 NHC(O)R₅;
 NHC(O)OR₆;
- 10 R₅= C₃-C₇-cycloalkyl;
- R₆= C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 15 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 above in R₂; or a pharmaceutically acceptable salt thereof
- with the proviso that when R₁=CH(CH₃)₂, and R₂=Ph, and X=CH, then R₃≠H, and
 20 n≠0, and R₄≠H, and Y≠OH, said process comprising:

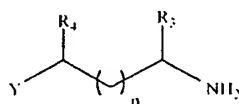
reacting a compound of the formula:



Formula XVII

with a compound of the formula:

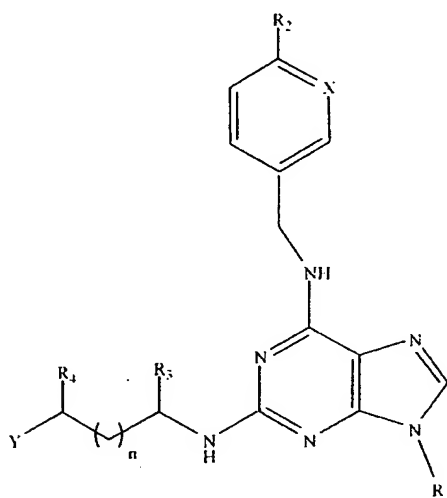
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Formula VIII

- 5 under conditions effective to form the purine derivative compound.

Another aspect of the present invention is directed to a process for preparation of a purine derivative compound of the formula:



Formula X

wherein:

10

R_1 are the same or different and independently selected from:

H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

15

X= N;
CH;

R_2 = phenyl;

20

substituted phenyl, wherein the substituents (1-2 in number) are in any position and are independently selected from R_1 , OR_1 , SR_1 , $S(O)R_1$, $S(O_2)R_1$, NHR_1 , NO_2 , $OC(O)CH_3$, $NHC(O)CH_3$, F, Cl, Br, CF_3 , $C(O)R_1$, $C(O)NHR_1$, phenyl, $C(O)NHCHR_1CH_2OH$;

25

1-naphthyl;
2-naphthyl;
heterocycles including:
2-pyridyl;
3-pyridyl;

4-pyridyl;
 5-pyrimidyl;
 thiophene-2-yl;
 thiophene-3-yl;
 5 2-furanyl;
 3-furanyl;
 2-benzofuranyl;
 benzothiophene-2-yl;
 2-pyrrolyl;
 10 3-pyrrolyl;
 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
 15 3-isoquinolinyl;
 4-isoquinolinyl;
 substituted heterocycle, wherein the substituents (1-2 in number) are in any
 position and are selected from Br, Cl, F, R₁, C(O)CH₃:

20 R₃ are the same or different and independently selected from:

H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 25 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 above in R₂:

R₄= H;
 30 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;

R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring:

35 n= 0-3;

Y= H;
 OR₁;
 NHR₁;
 40 NHC(O)R₃;
 NHSO₂R₃;
 NHC(O)NHR₃;
 NHC(O)R₅;
 NHC(O)OR₆;

45 R₅= C₃-C₇-cycloalkyl;

R₆= C₁-C₄-straight chain alkyl;

C₃-C₄-branched chain alkyl:

C₂-C₄-alkenyl chain:

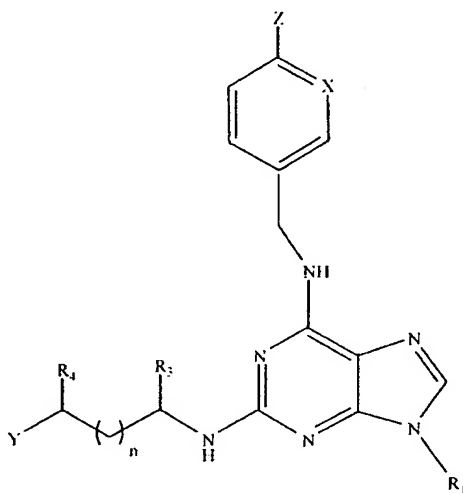
(CH₂)_nPh;

5 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined above in R₂; or a pharmaceutically acceptable salt thereof.

with the proviso that when R₁ = CH(CH₃)₂ and R₂ = Ph and X = CH, then R₃ ≠ H, and n ≠ 0, and R₄ ≠ H, and Y ≠ OH, said process comprising:

reacting a compound of the formula:

10



Formula IX

wherein

Z = Br or I

15 with a compound of the formula: R₂-B(OH)₂, R₂-Sn(n-Bu)₃, R₂-Sn(Me)₃, or mixtures thereof, under conditions effective to form the purine derivative compound.

The compounds of the present invention, as described in Formula I, show significantly improved growth inhibition of human transformed cell lines and/or cyclin/cdk inhibition relative to compounds of the prior art. These compounds have
20 been demonstrated to be potent growth inhibitors in dozens of human transformed cell lines. Olomoucine, a structurally related purine derivative, is a poor human transformed cell growth inhibition agent with GI₅₀ values in the 20,000-100,000 nM range over 60-transformed cell lines. By contrast, the compounds of the present invention demonstrate GI₅₀ values over 60-transformed cell lines in the <10-25,000

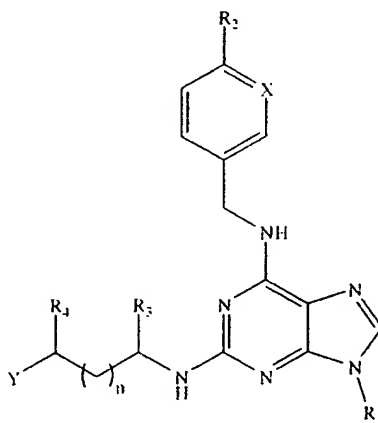
nM range, preferably in the <10-100 nM range over 60-transformed cell lines, and, most preferably, <10 nM across 60-human transformed cell lines. This finding is unexpected from the prior art, which specifically teaches that compounds of the present invention would not be potent human transformed cell line growth inhibitors.

5 The R₂ group in Formula I imparts unexpected and significant improvement in growth inhibition in human transformed cell lines, while substitution of various groups at R₃ and R₄ found in Formula I impart important features that contribute to cyclin/cdk inhibition and growth inhibition of human transformed cell lines. Specifically, the combination of the R₂ group and the substitutions within R₃ and R₄ result in compounds with superior biological activity. Compounds which are
10 cyclin/cdk inhibitors and/or human transformed cell line growth inhibitors have utility in treating human proliferative cellular disorders.

DETAILED DESCRIPTION OF THE INVENTION

15

The compounds of the present invention are represented by the chemical structure found in Formula II.



Formula II

20

wherein:

R₁ are the same or different and independently selected from:

- 25 H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;

X= N;
CH:

5 R₂= phenyl;
substituted phenyl, wherein the substituents (1-2 in number) are in any
position and independently selected from R₁, OR₁, SR₁, S(O)R₁,
S(O₂)R₁, NHR₁, NO₂, OC(O)CH₃, NHC(O)CH₃, F, Cl, Br, CF₃, C(O)R₁,
C(O)NHR₁, phenyl, C(O)NHCHR₁CH₂OH;
10 1-naphthyl;
2-naphthyl;
heterocycles including:
2-pyridyl;
3-pyridyl;
4-pyridyl;
15 5-pyrimidyl;
thiophene-2-yl;
thiophene-3-yl;
2-furanyl;
3-furanyl;
20 2-benzofuranyl;
benzothiophene-2-yl;
2-pyrrolyl;
3-pyrrolyl;
2-quinolinyl;
25 3-quinolinyl;
4-quinolinyl;
1-isoquinolinyl;
3-isoquinolinyl;
4-isoquinolinyl;
30 substituted heterocycle, wherein the substituents (1-2 in number) are in any
position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

R₃ are the same or different and independently selected from:

35 H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

40 R₄= H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring;

45 n= 0-3;

Y= H;
OR₁;
NHR₁;

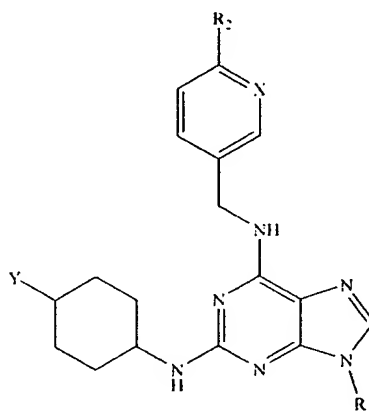
NHC(O)R_3 ;

NHSO_2R_3 ;

NHC(O)NHR_3 ; or a pharmaceutically acceptable salt thereof;

- 5 with the proviso that when $\text{R}_1=\text{CH}(\text{CH}_3)_2$, and $\text{R}_2=\text{Ph}$, and $\text{X}=\text{CH}$, then $\text{R}_3\neq\text{H}$, and $n\neq 0$, and $\text{R}_4\neq\text{H}$, and $\text{Y}\neq\text{OH}$.

More preferably, the compounds of the current invention are represented by the chemical structure found in Formula III.



Formula III

wherein:

- 15 R_1 are the same or different and independently selected from:

H;

C_1 - C_4 -straight chain alkyl;

C_3 - C_4 -branched chain alkyl;

- 20 $\text{X} =$ N;
CH;

$\text{R}_2 =$ phenyl;

substituted phenyl, wherein the substituents (1-2 in number) are in any

- 25 position and independently selected from R_1 , OR_1 , SR_1 , S(O)R_1 , $\text{S(O}_2\text{)R}_1$, NHR_1 , NO_2 , OC(O)CH_3 , NHC(O)CH_3 , F, Cl, Br, CF_3 , C(O)R_1 , C(O)NHR_1 , phenyl, $\text{C(O)NHCHR}_1\text{CH}_2\text{OH}$;

heterocycles including:

- 30 2-pyridyl;
3-pyridyl;
4-pyridyl;
5-pyrimidyl;
thiophene-2-yl;
thiophene-3-yl;
35 2-furanyl;
3-furanyl;

2-benzofuranyl;
 benzothiophene-2-yl;
 2-pyrrolyl;
 3-pyrrolyl;
 5 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
 3-isoquinolinyl;
 10 4-isoquinolinyl;
 substituted heterocycle, wherein the substituents (1-2 in number) are in any position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

Y= OR₁;
 15 NHR₁;
 NHC(O)R₁;
 NHSO₂R₁;
 HC(O)NHR₁;
 NHC(O)OR₆; or a pharmaceutically acceptable salt thereof;

20 R₆ = C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 or a pharmaceutically acceptable salt thereof.

25 In another embodiment, the present invention is directed to a method for inhibiting cellular proliferation in mammals comprising administering a therapeutically effective amount of the compound of the present invention to the mammal.

30 The compounds of the present invention can be administered orally, parenterally, for example, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, or by application to mucous membranes, such as, that of the nose, throat, and bronchial tubes. They may be administered alone or with suitable pharmaceutical carriers, and can be in solid or liquid form such as,

35 tablets, capsules, powders, solutions, suspensions, or emulsions.

Based on the results obtained in the standard pharmacological test procedures described below, the compounds of the present invention are useful as antineoplastic agents. More particularly, the compounds of the present invention are useful for inhibiting the growth of neoplastic cells, causing cell death of neoplastic

40 cells, and eradicating neoplastic cells. The compounds of the present invention are, therefore, useful for treating solid tumors, including sarcomas and carcinomas, such

as astrocytomas, prostate cancer, breast cancer, small cell lung cancer, and ovarian cancer, leukemias, lymphomas, adult T-cell leukemia/lymphoma, and other neoplastic disease states.

5 In addition to the utilities described above, many of the compounds of the present invention are useful in the preparation of other compounds.

The active compounds of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral
10 therapeutic administration, these active compounds may be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compound in these compositions may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of
15 the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the present invention are prepared so that an oral dosage unit contains between about 1 and 250 mg of active compound.

The tablets, capsules, and the like may also contain a binder such as
20 gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

25 Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar, or both. A syrup may contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

30 These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be

prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or
5 polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous
10 preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol
15 (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds of the present invention may also be administered directly to the airways in the form of an aerosol. For use as aerosols, the compounds of the present invention in solution or suspension may be packaged in a pressurized
20 aerosol container together with suitable propellants, for example, hydrocarbon propellants like propane, butane, or isobutane with conventional adjuvants. The materials of the present invention also may be administered in a non-pressurized form such as in a nebulizer or atomizer.

25 **General Synthetic Schemes**

The compounds of the present invention can be prepared by conventional methods of organic synthesis practiced by those skilled in the art. The general reaction sequences outlined below are general methods useful for preparing the compounds of the present invention and are not meant to be limiting in scope or
30 utility.

Reaction of 2,6-dichloropurine (**Formula IV**) with various amines of **Formula V** in the presence of a polar solvent, such as ethanol, provides purines of

Formula VI (General Flowsheet I, *infra*). Reaction of purines of **Formula VI** with alkyl halides (R_1-Z) in the presence of a base such as potassium carbonate provides N1-alkylated purines of **Formula VII**. Chloride displacement with N-alkylated purines of **Formula VII** with amines of structure **Formula VIII** in an inert solvent
 5 such as ethanol or butanol at an appropriate temperature provides purines of **Formula IX**. Transition metal-mediated cross-coupling reaction of purines of **Formula IX** with boronic acid ($R_2-B(OH)_2$) or tin reagents ($R_2-Sn(n-Bu)_3$ or R_2-SnMe_3) provides purines of **Formula X**. If in **Formula X** ($Y=NH_2$), then subsequent reaction of **Formula X** ($Y=NH_2$) with acid chloride (R_3COCl), or sulfonyl chloride (R_3SO_2Cl),
 10 or isocyanate (R_3NCO), or chloroformate ($ClC(O)OR_6$) reagents provides purines of **Formula XI** wherein $Y=NHC(O)R_3$, $NHSO_2R_3$, or $NHC(O)NHR_3$, or $NHC(O)OR_6$, respectively. On the other hand, if in **Formula X**, Y already is OR_1 or $NHC(O)R_3$ or $NHSO_2R_3$ or $NHC(O)NHR_3$ or $NHC(O)OR_6$, as a result of what Y started out as in **Formula VIII**, then this last step is unnecessary.

15

Definitions of the groups include:

R_1 are the same or different and independently selected from:

20 H;
 C_1-C_4 -straight chain alkyl;
 C_3-C_4 -branched chain alkyl;

Z= Br;
 I;

25 R_2 = phenyl;
 substituted phenyl, wherein the substituents (1-2 in number) are in any position and independently selected from R_1 , OR_1 , SR_1 , $S(O)R_1$, $S(O_2)R_1$, NHR_1 , NO_2 , $OC(O)CH_3$, $NHC(O)CH_3$, F, Cl, Br, CF_3 , $C(O)R_1$, $C(O)NHR_1$, phenyl, $C(O)NHCHR_1CH_2OH$;
 30 1-naphthyl;
 2-naphthyl;
 heterocycles including:
 2-pyridyl;
 3-pyridyl;
 35 4-pyridyl;
 5-pyrimidyl;
 thiophene-2-yl;
 thiophene-3-yl;
 2-furanyl;
 40 3-furanyl;

- 5 2-benzofuranyl;
 benzothiophene-2-yl;
 2-pyrrolyl;
 3-pyrrolyl;
 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
10 3-isoquinolinyl;
 4-isoquinolinyl;
 substituted heterocycle, wherein the substituents (1-2 in number) are in any
 position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

R₃ are the same or different and independently selected from:

5 H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 above in R₂:

10 R₄= H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl:

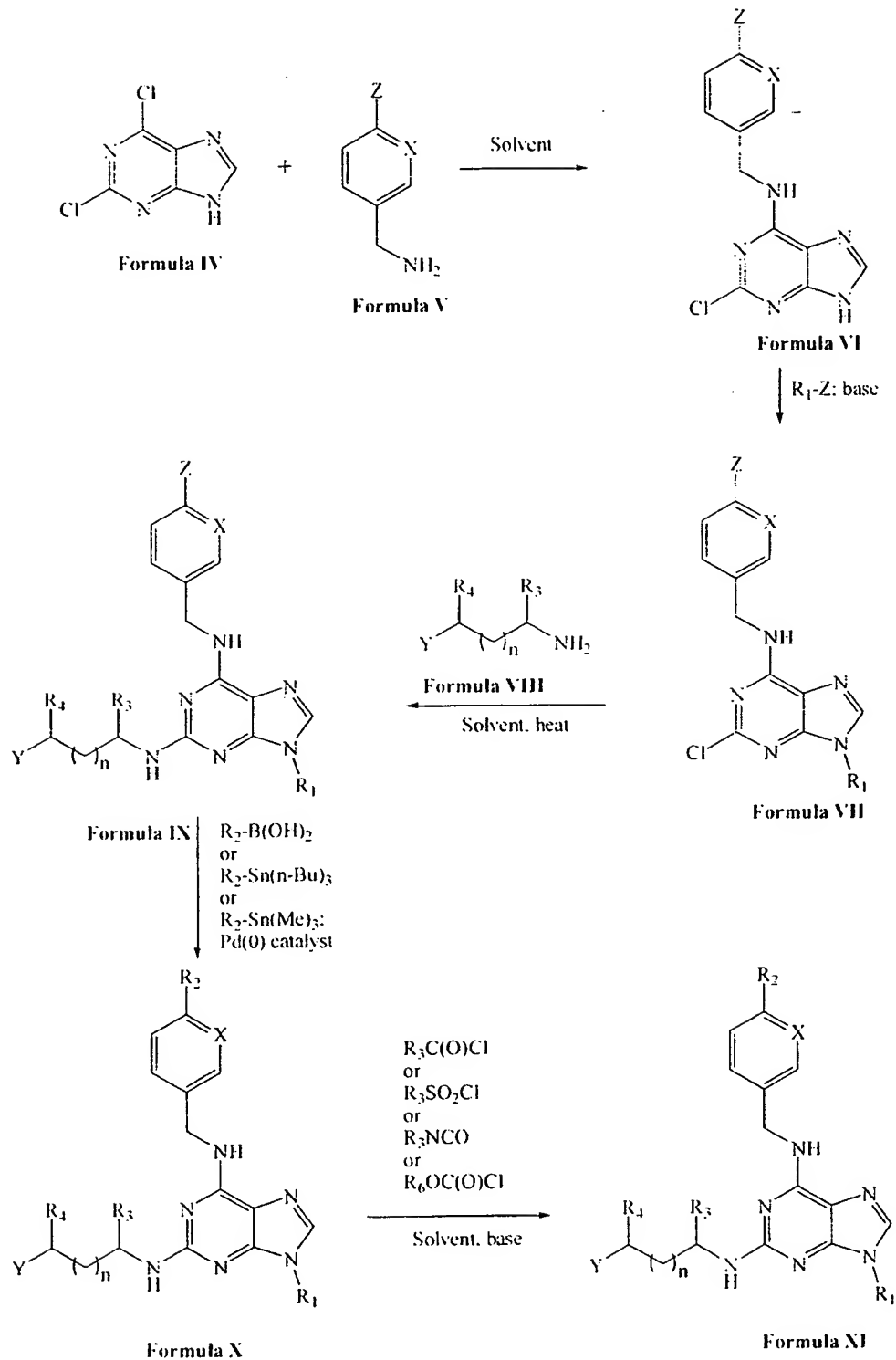
R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring:

15. n= 0-3;

20 Y= H;
 OR₁;
 NHR₁;
 NHC(O)R₃;
 NHSO₂R₃;
 NHC(O)NHR₃;
 NHC(O)OR₆;

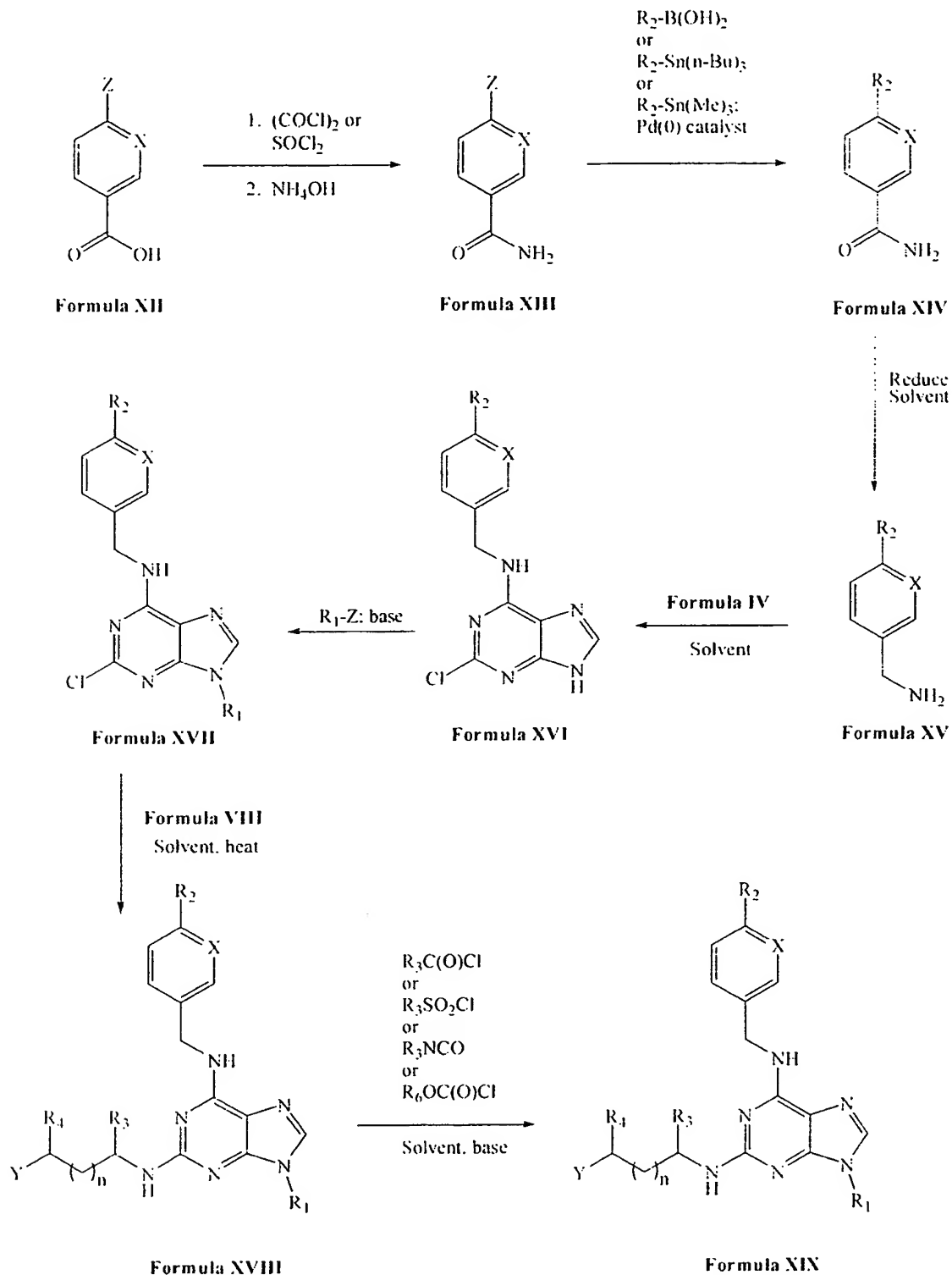
25 R₆= C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₃-C₇-cycloalkyl;
 C₂-C₄-alkenyl chain;
 (CH₂)_nPh;
 30 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 above in R₂.

General Flowsheet I



General non-limiting syntheses of compounds of the present invention of **Formula XVIII** and **Formula XIX** are shown below.

General Flowsheet II



Reaction of acids of **Formula XII** with oxalyl chloride or thionyl chloride followed by reaction with ammonium hydroxide provides amides of **Formula XIII** (General Flowsheet II). Transition metal-mediated cross-coupling reaction of amides of **Formula XIII** with boronic acid ($R_2-B(OH)_2$) or tin reagents ($R_2-Sn(n-Bu)_3$) or (R_2-SnMe_3) provides amides of **Formula XIV**. Reduction of amides of **Formula XIV** with a reducing agent in an appropriate solvent provides amines of **Formula XV**. Reaction of amines of **Formula XV** with 2,6-dichloropurine (**Formula IV**) in the presence of a polar solvent, such as ethanol, provides purines of **Formula XVI**. Reaction of purines of **Formula XVI** with alkyl halides (R_1-Z) in the presence of a base such as potassium carbonate provides N1-alkylated purines of **Formula XVII**. Chloride displacement of purines of **Formula XVII** with amines of **Formula VIII** in an inert solvent such as ethanol or butanol at an appropriate temperature provides purines of **Formula XVIII**. If in **Formula XVIII** ($Y=NH_2$), then subsequent reaction of **Formula XVIII** ($Y=NH_2$) with acid chloride R_3COCl , or sulfonyl chloride (R_3SO_2Cl), or isocyanate (R_3NCO), or chloroformate ($ClC(O)OR_6$) reagents provides purines of **Formula XIX** wherein $Y=NHC(O)R_3$, or $NHSO_2R_3$, or $NHC(O)NHR_3$, or $NHC(O)OR_6$, respectively. On the other hand, if in **Formula XVIII**, Y already is OR_1 or $NHC(O)R_3$ or $NHSO_2R_3$ or $NHC(O)NHR_3$ or $NHC(O)OR_6$, as a result of what Y started out as in **Formula VIII**, then this last step is unnecessary.

Definitions of the groups include:

R_1 are the same or different and independently selected from:

- H;
- C₁-C₄-straight chain alkyl;
- C₃-C₄-branched chain alkyl;

X= N;
CH;

Z= Br;
I;

R_2 = phenyl;
substituted phenyl, wherein the substituents (1-2 in number) are in any position and independently selected from R_1 , OR_1 , SR_1 , $S(O)R_1$,

- 26 -

S(O₂)R₁, NHR₁, NO₂, OC(O)CH₃, NHC(O)CH₃, F, Cl, Br, CF₃, C(O)R₁,
C(O)NHR₁, phenyl, C(O)NHCHR₁CH₂OH;

1-naphthyl;

2-naphthyl;

5 heterocycles including:

2-pyridyl;

3-pyridyl;

4-pyridyl;

5-pyrimidyl;

10 thiophene-2-yl;

thiophene-3-yl;

2-furanyl;

3-furanyl;

2-benzofuranyl;

15 benzothiophene-2-yl;

2-pyrrolyl;

3-pyrrolyl;

2-quinolinyl;

3-quinolinyl;

20 4-quinolinyl;

1-isoquinolinyl;

3-isoquinolinyl;

4-isoquinolinyl;

25 substituted heterocycle, wherein the substituents (1-2 in number) are in any
position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

R₃ are the same or different and independently selected from:

H;

C₁-C₄-straight chain alkyl;

30 C₃-C₄-branched chain alkyl;

C₂-C₄-alkenyl chain;

(CH₂)_nPh;

(CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined

above in R₂;

35

R₄= H;

C₁-C₄-straight chain alkyl;

C₃-C₄-branched chain alkyl;

40 R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring;

n= 0-3;

Y= H;

45 OR₁;

NHR₁;

NHC(O)R₃;

NHSO₂R₃;

NHC(O)NHR_3 :

NHC(O)OR_6 :

- 5 $\text{R}_6 =$ $\text{C}_1\text{-C}_4\text{-straight chain alkyl}$;
 $\text{C}_3\text{-C}_4\text{-branched chain alkyl}$;
 $\text{C}_3\text{-C}_7\text{-cycloalkyl}$;
 $\text{C}_2\text{-C}_4\text{-alkenyl chain}$;
 $(\text{CH}_2)_n\text{Ph}$;
 $(\text{CH}_2)_n\text{-substituted phenyl}$, wherein the phenyl substituents are as defined
10 above in R_2 .

Scheme 1

1

EtOH

2

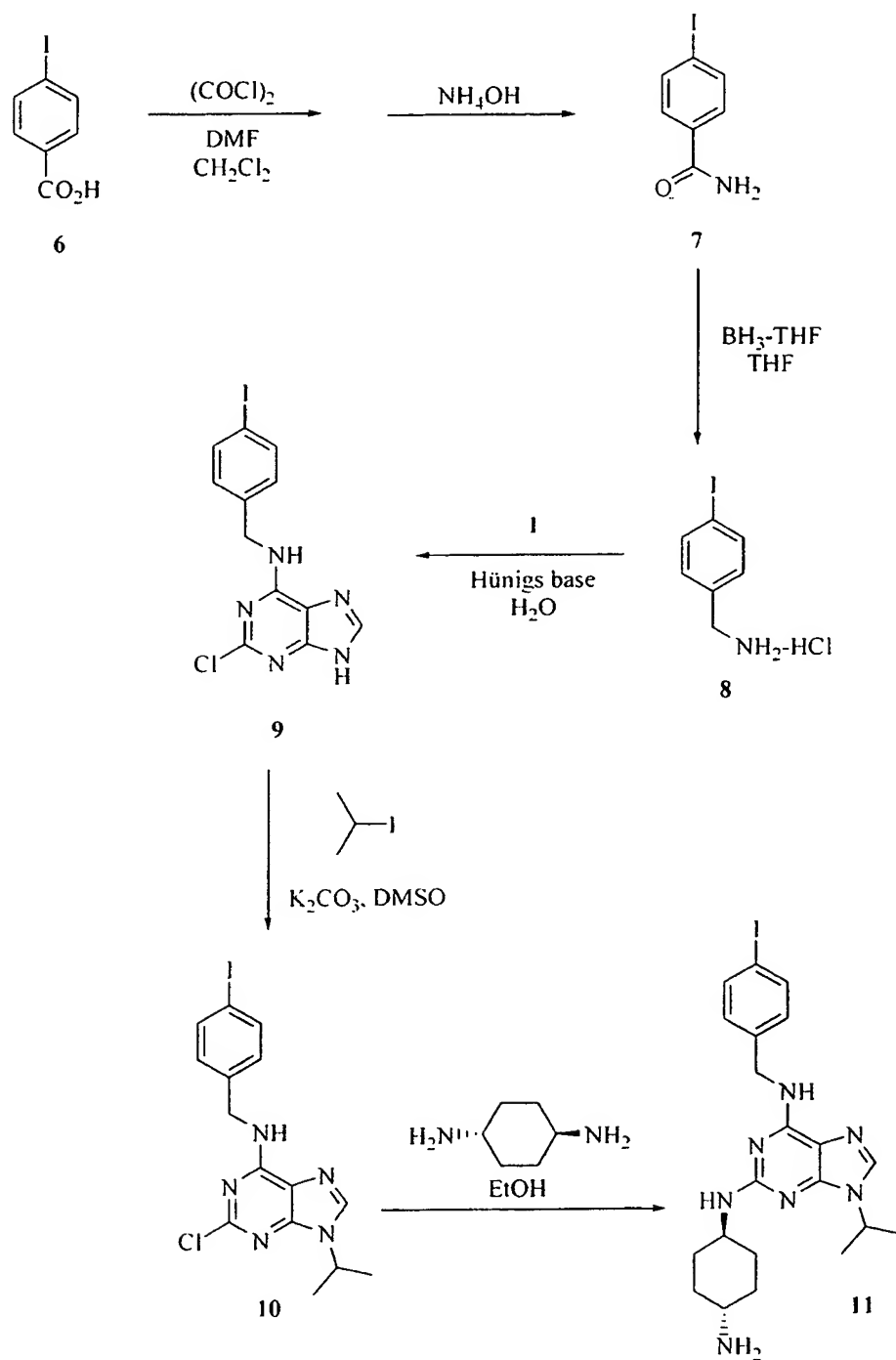
3

4

5

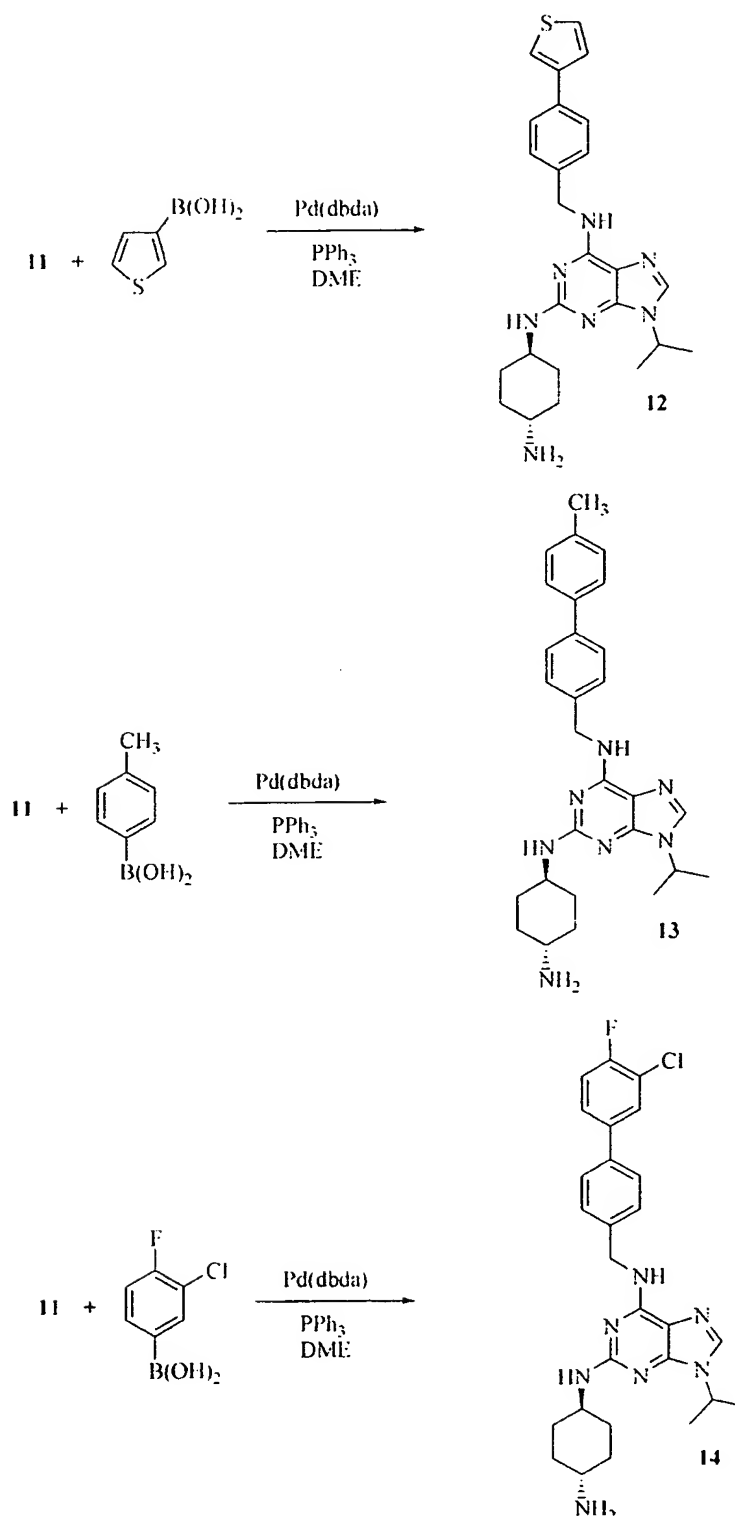
The synthesis of compound **11** is shown below in Scheme II.

Scheme II



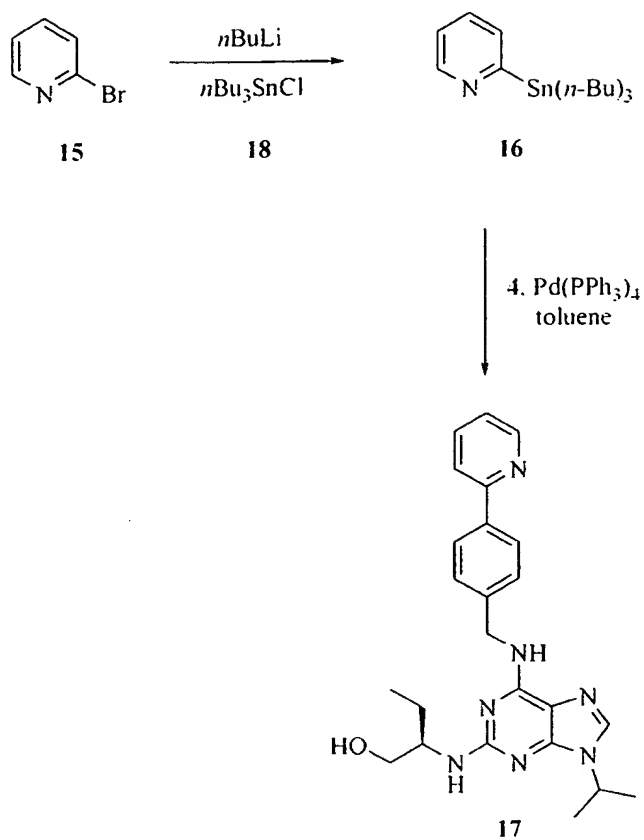
The syntheses of compounds **12**, **13** and **14** are shown below in Scheme III.

Scheme III



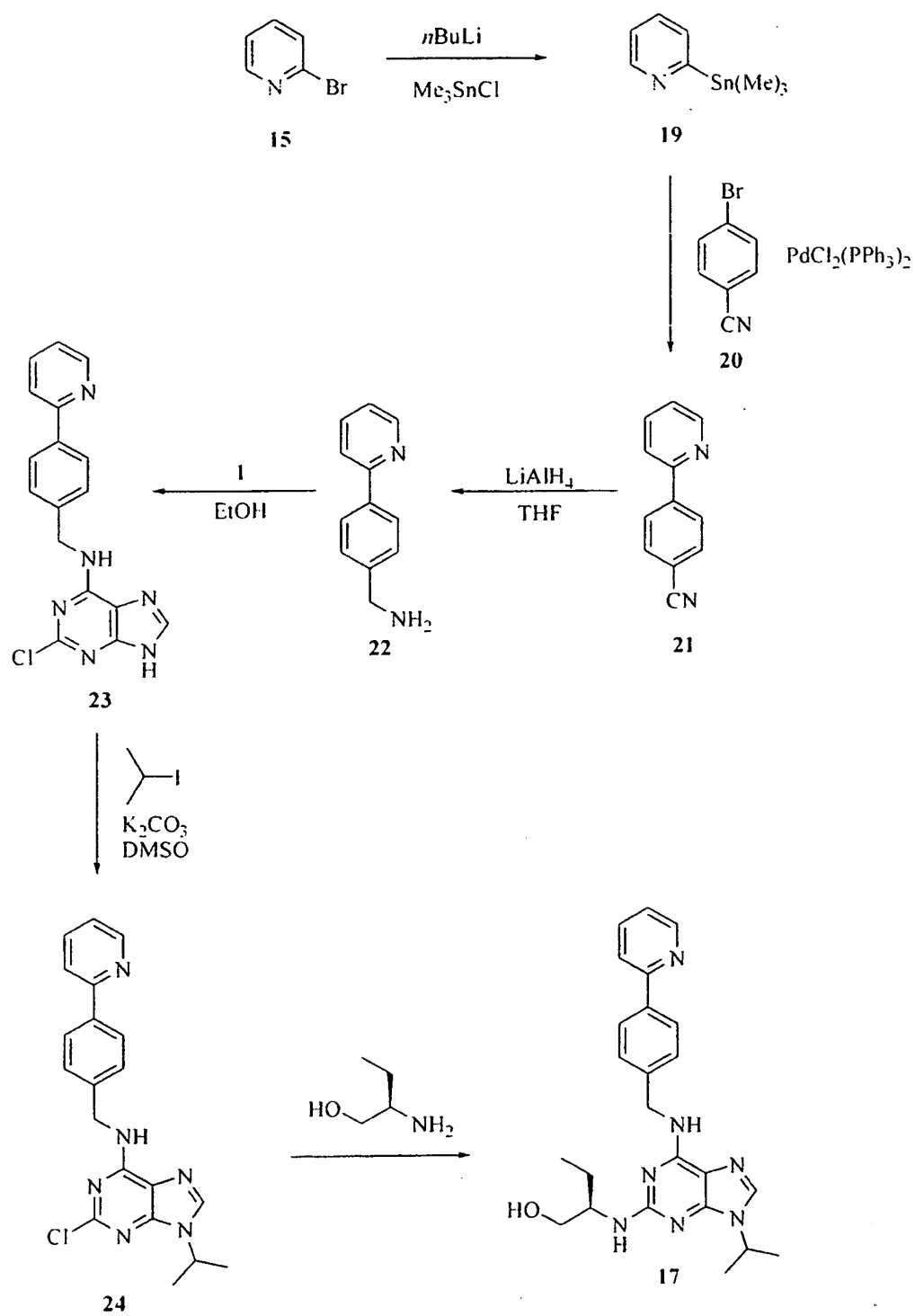
The synthesis of compound **17** is shown below in Scheme IV.

Scheme IV



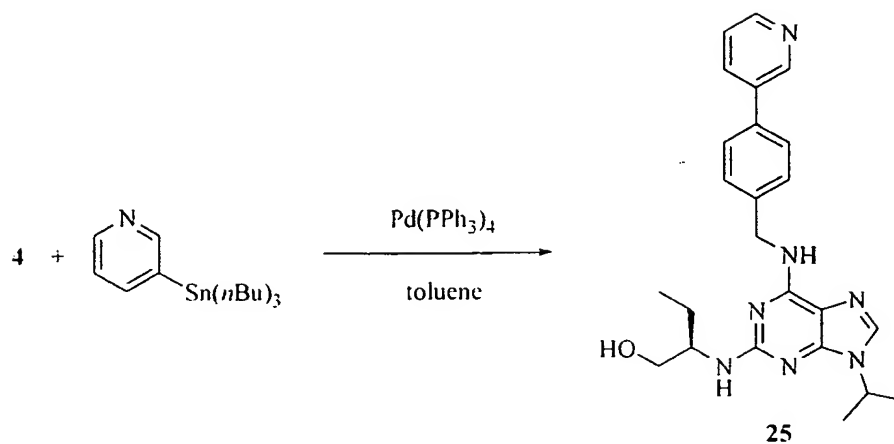
The synthesis of compound 17 is shown below in Scheme V.

Scheme V



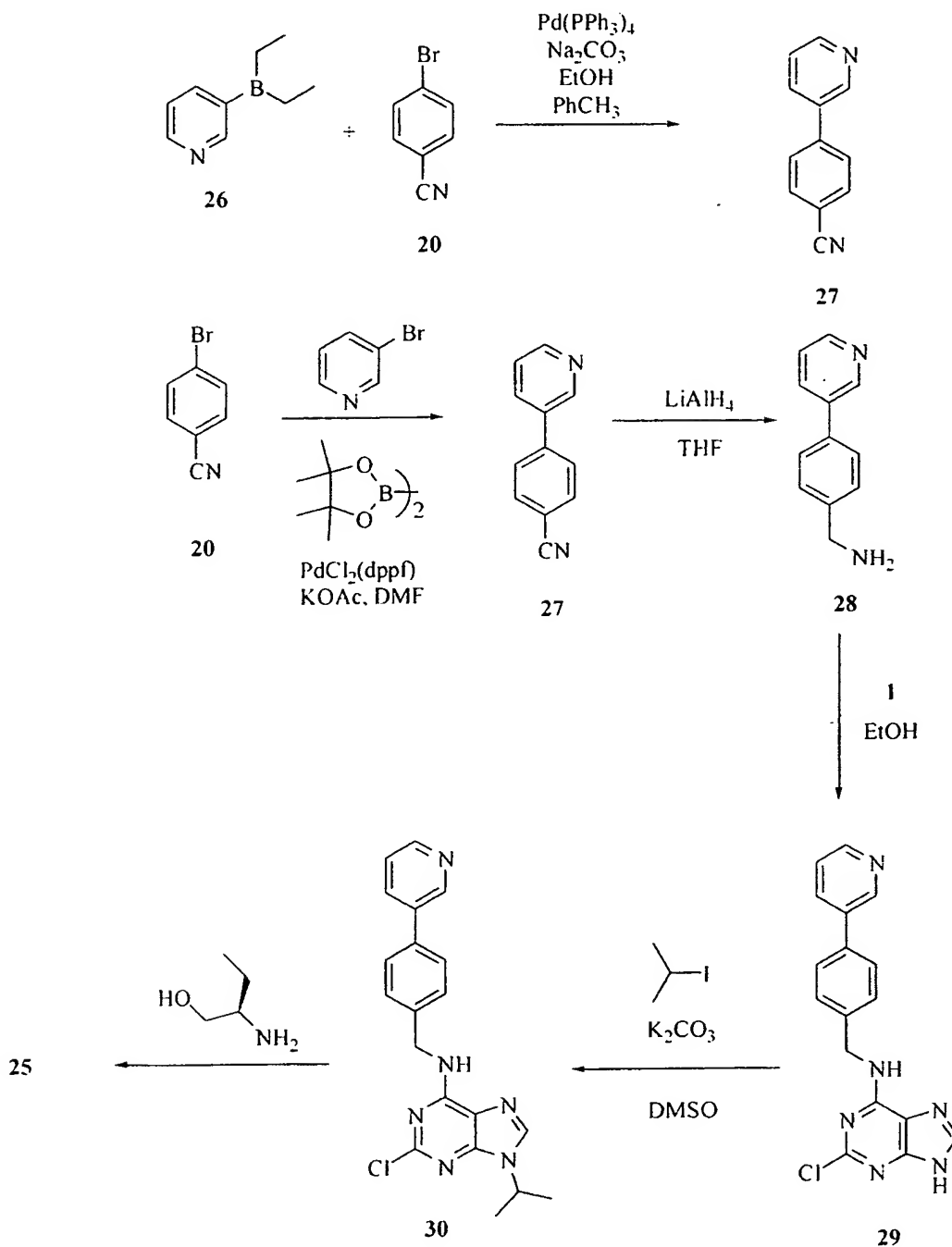
The synthesis of compound **25** is shown below in Scheme VI.

Scheme VI



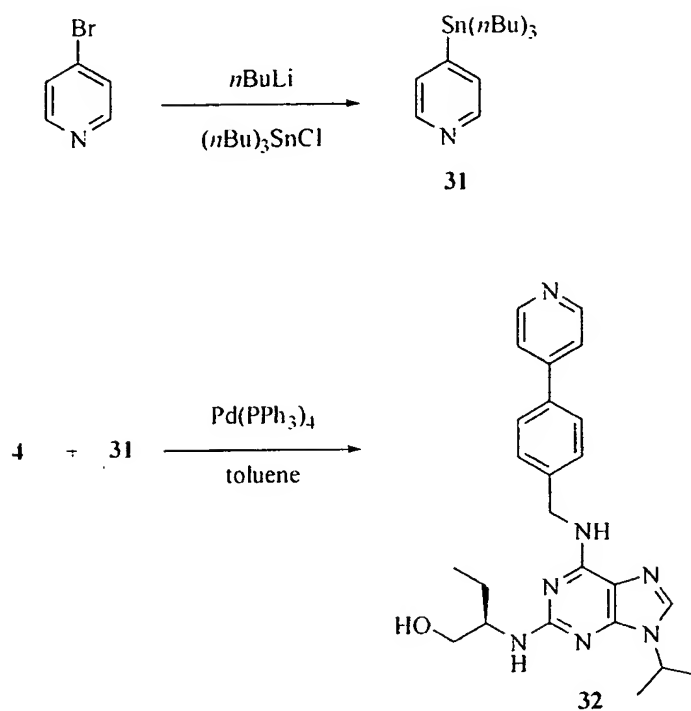
An alternative synthesis of compound **25** is shown below in Scheme VII.

Scheme VII



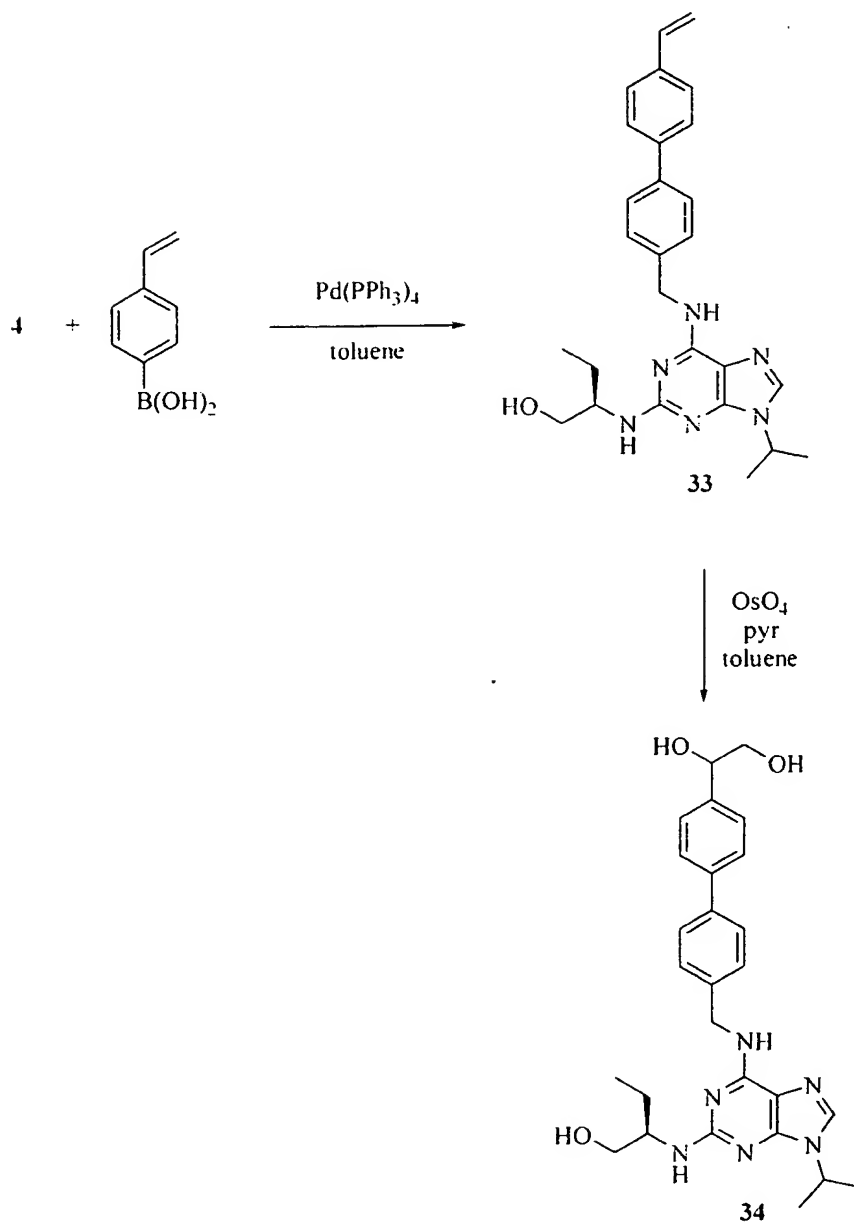
The synthesis of compound **32** is shown below in Scheme VIII.

Scheme VIII



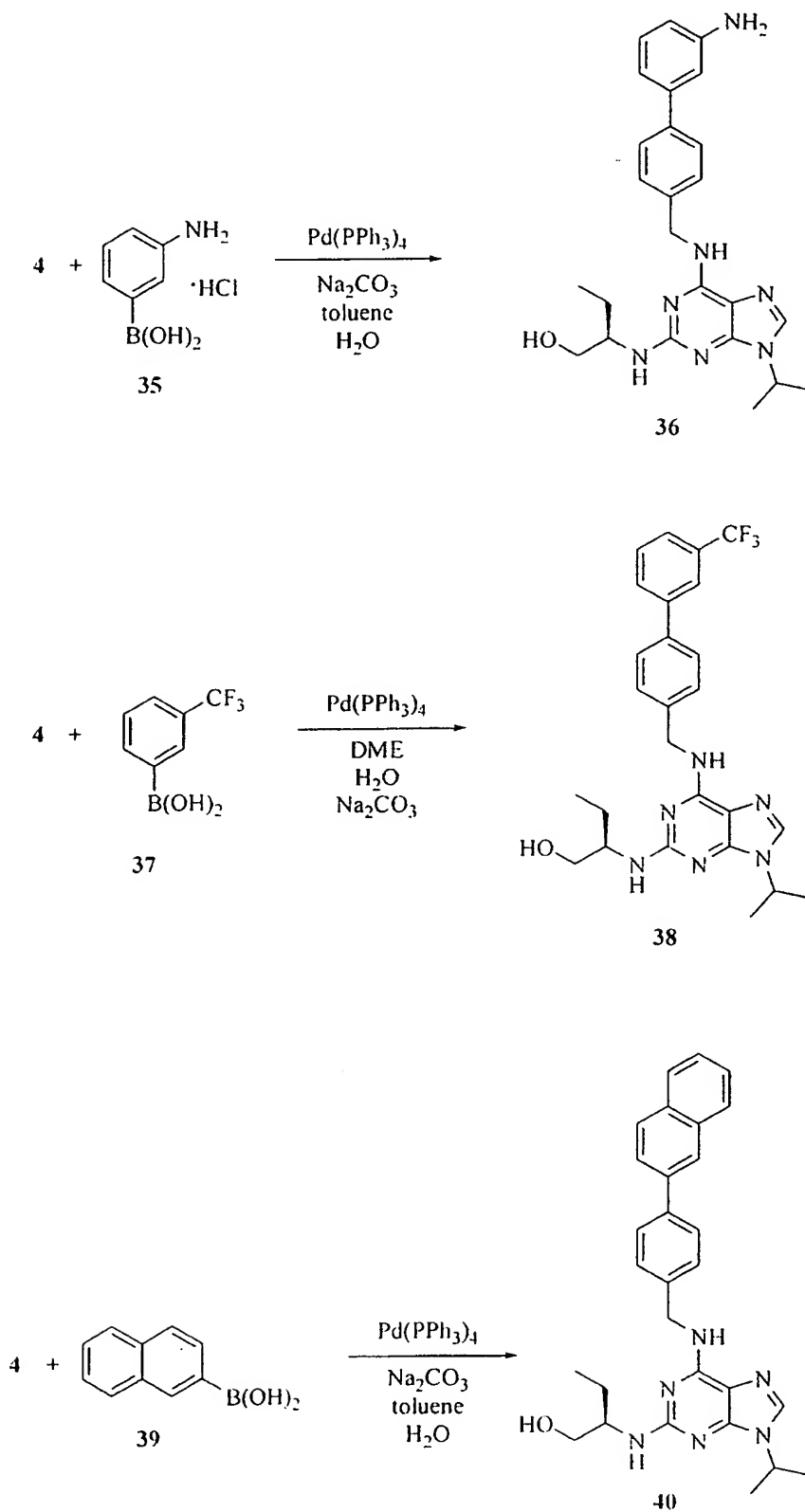
The syntheses of compounds **33** and **34** are shown below in Scheme IX.

Scheme IX



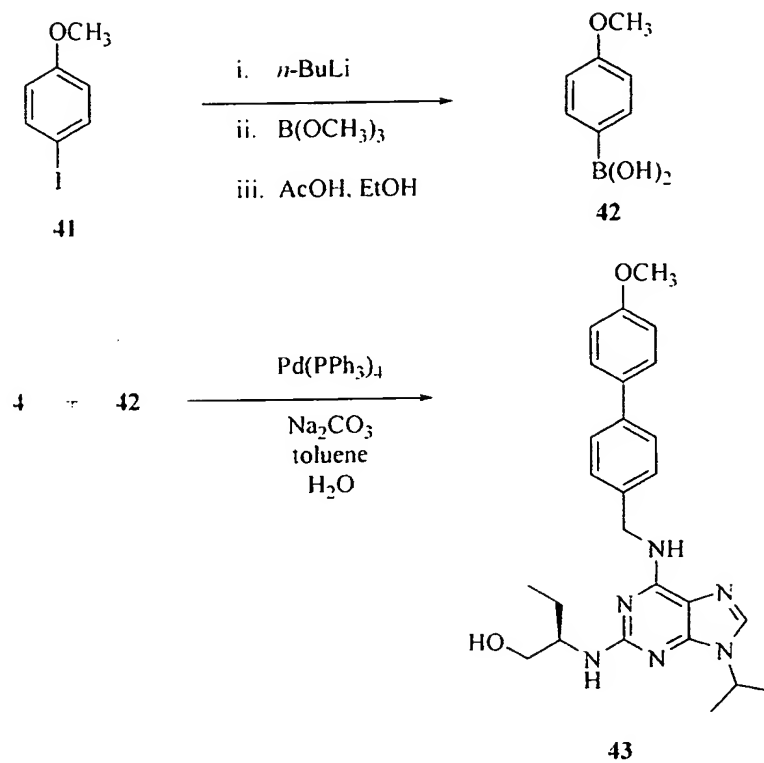
The syntheses of compounds 36, 38, and 40 are shown below in Scheme X.

Scheme X



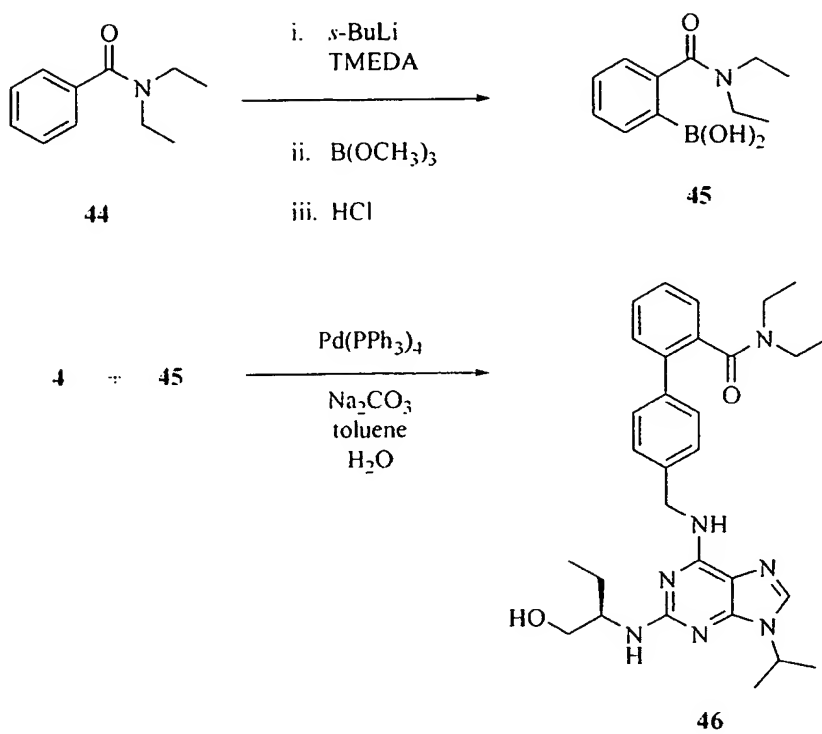
The synthesis of compound 43 is shown below in Scheme XI.

Scheme XI



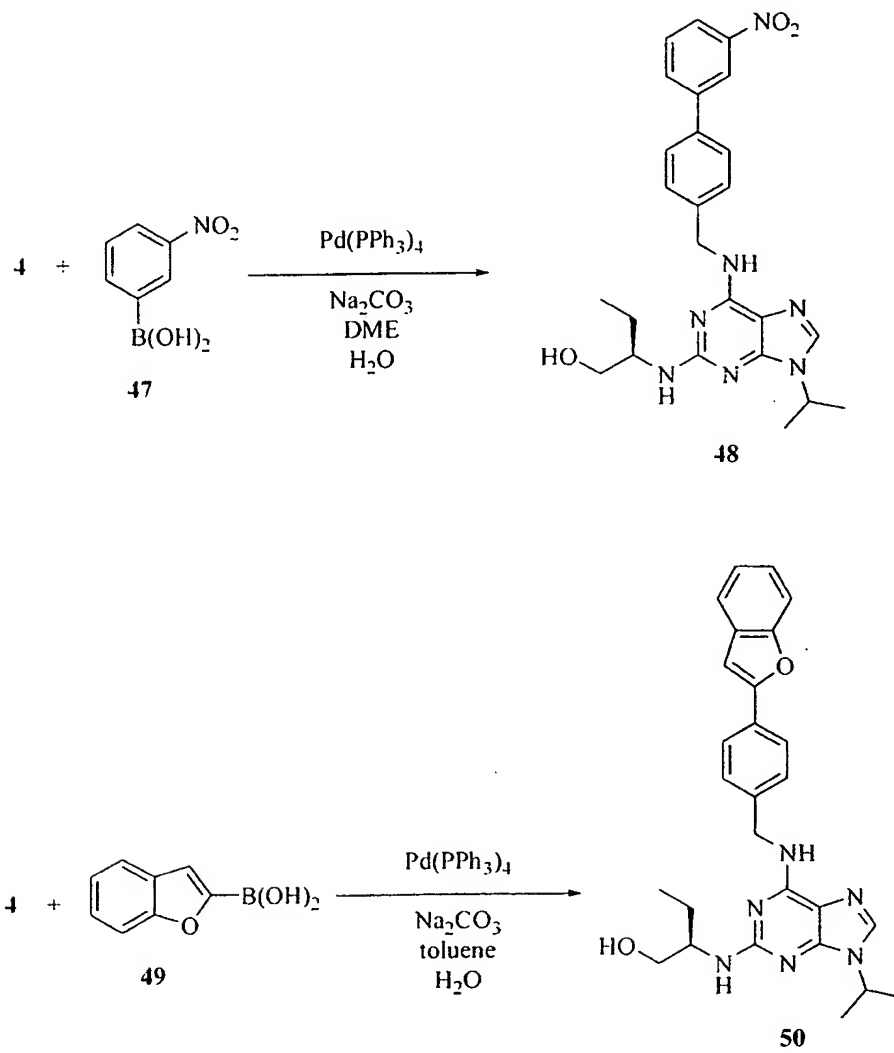
The synthesis of compound **46** is shown below in Scheme XII.

Scheme XII



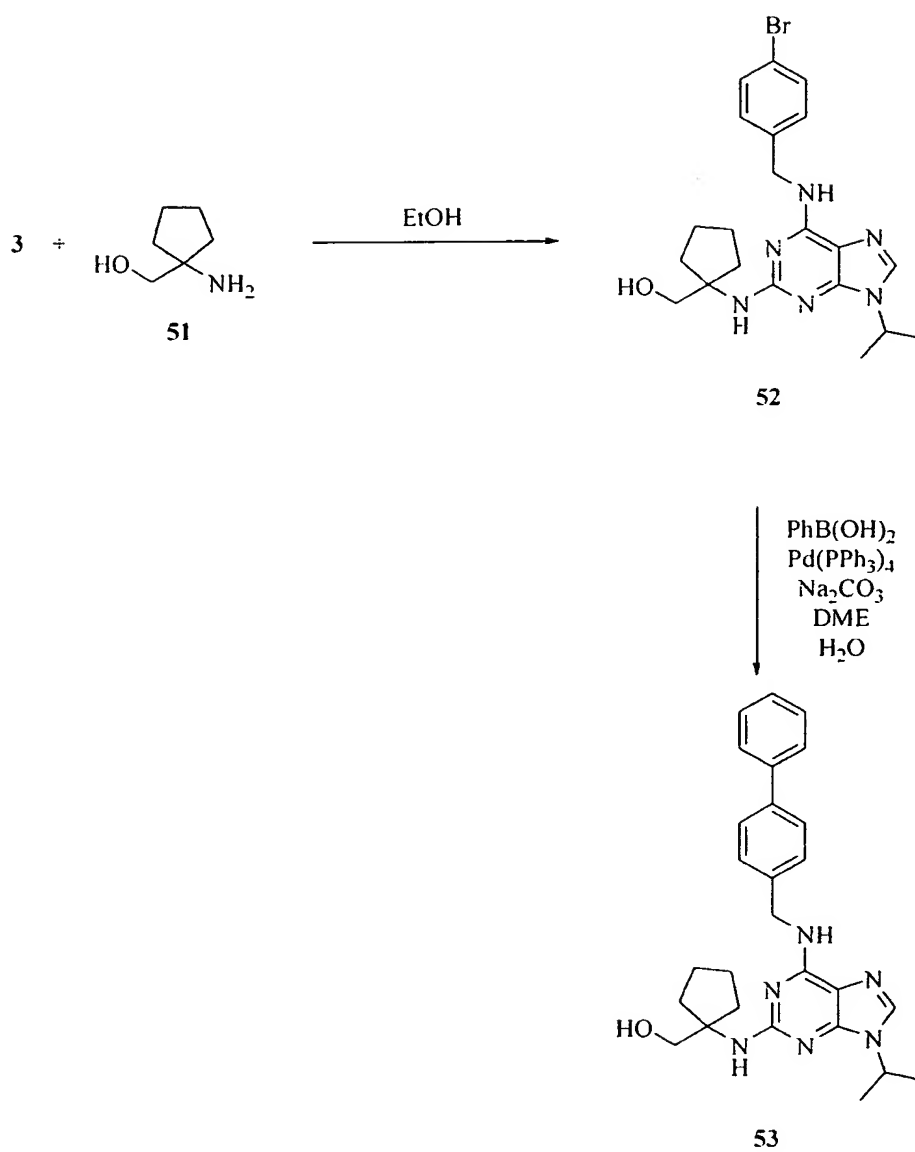
The syntheses of compound **48** and **50** are shown below in Scheme XIII.

Scheme XIII



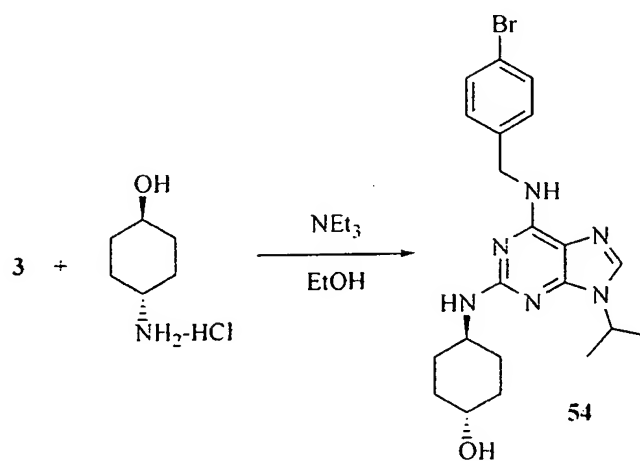
The synthesis of compound **53** is shown below in Scheme XIV.

Scheme XIV



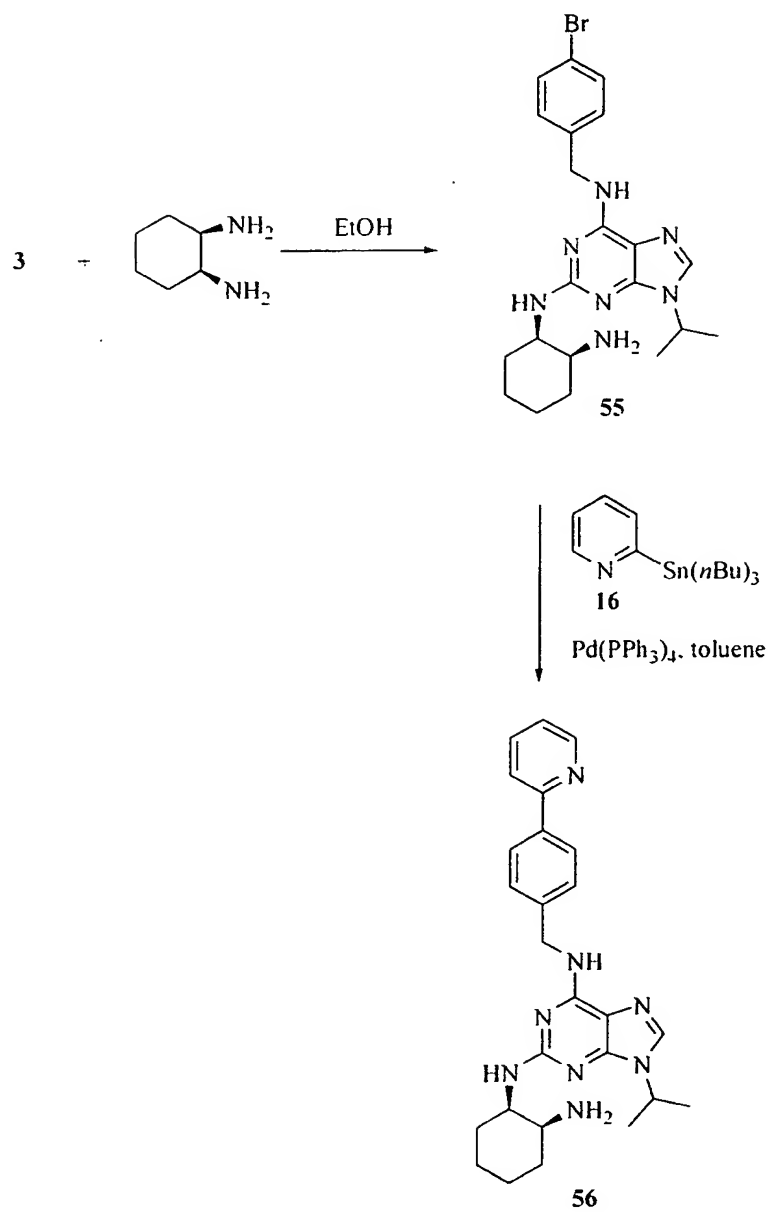
The synthesis of compound **54** is shown below in Scheme XV.

Scheme XV



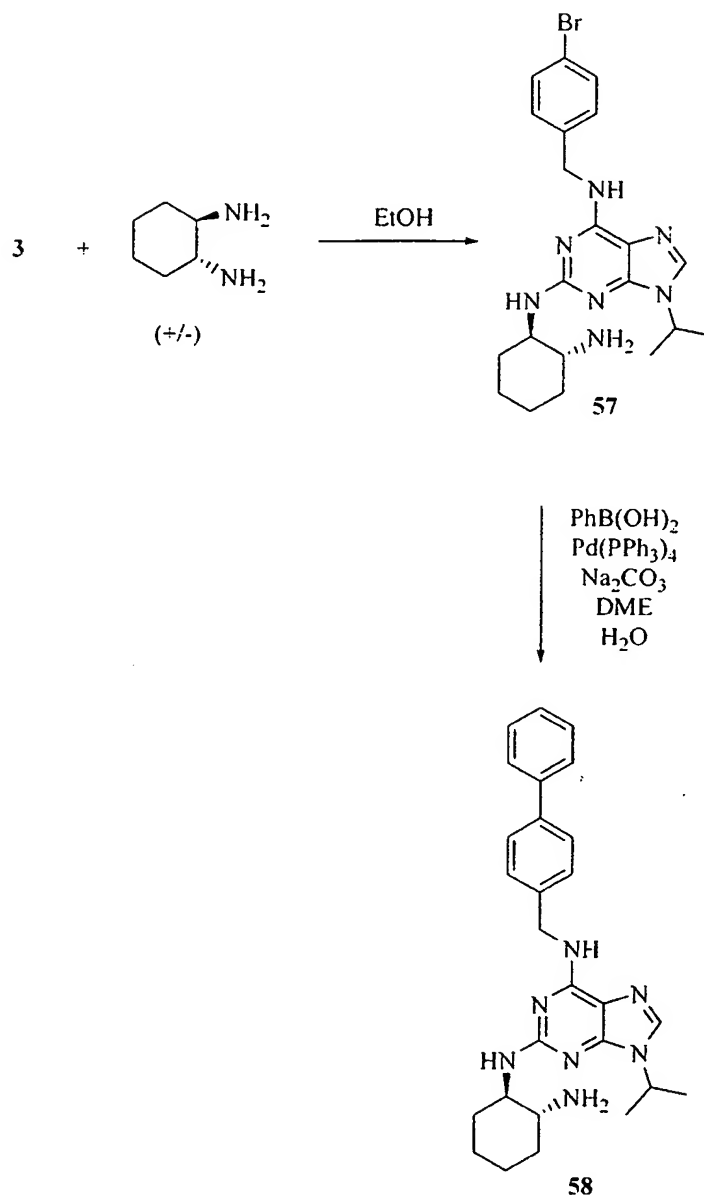
The synthesis of compound **56** is shown below in Scheme XVI.

Scheme XVI



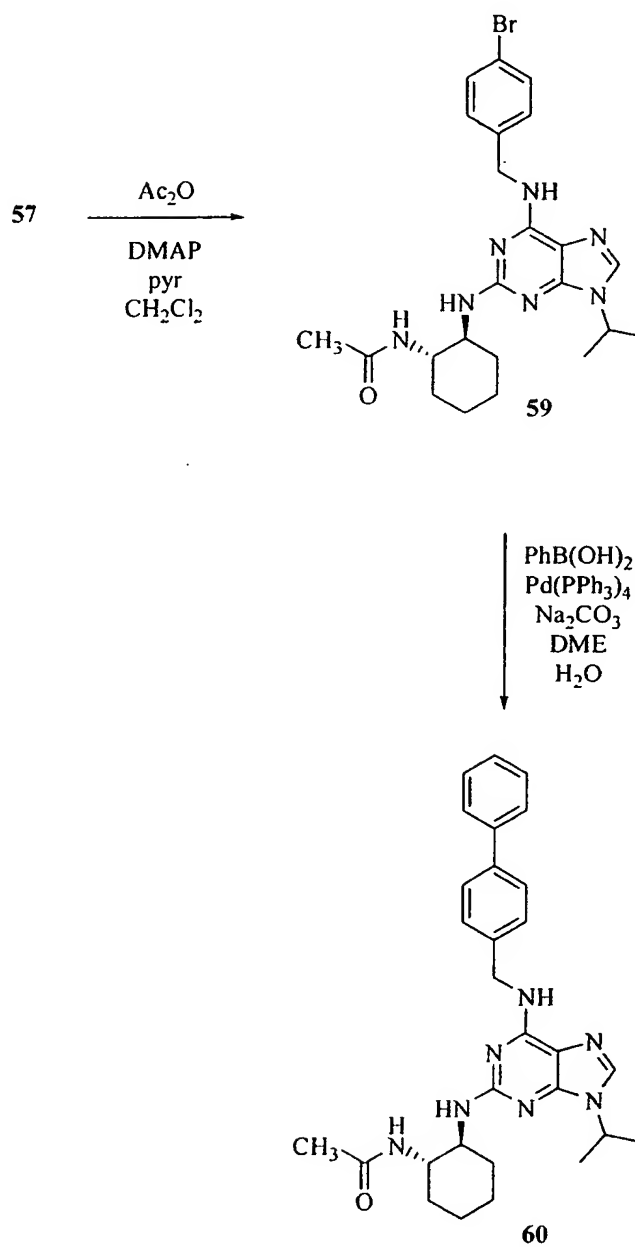
The synthesis of compound **58** is shown below in Scheme XVII.

Scheme XVII



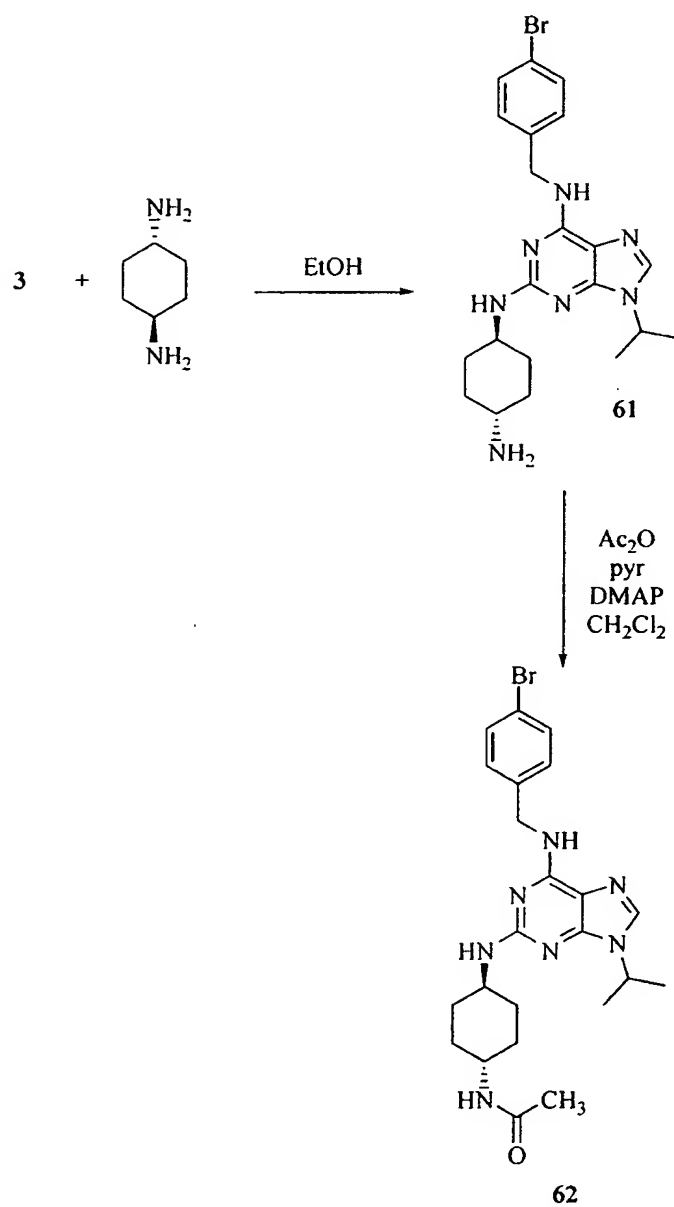
The synthesis of compound **60** is shown below in Scheme XVIII.

Scheme XVIII



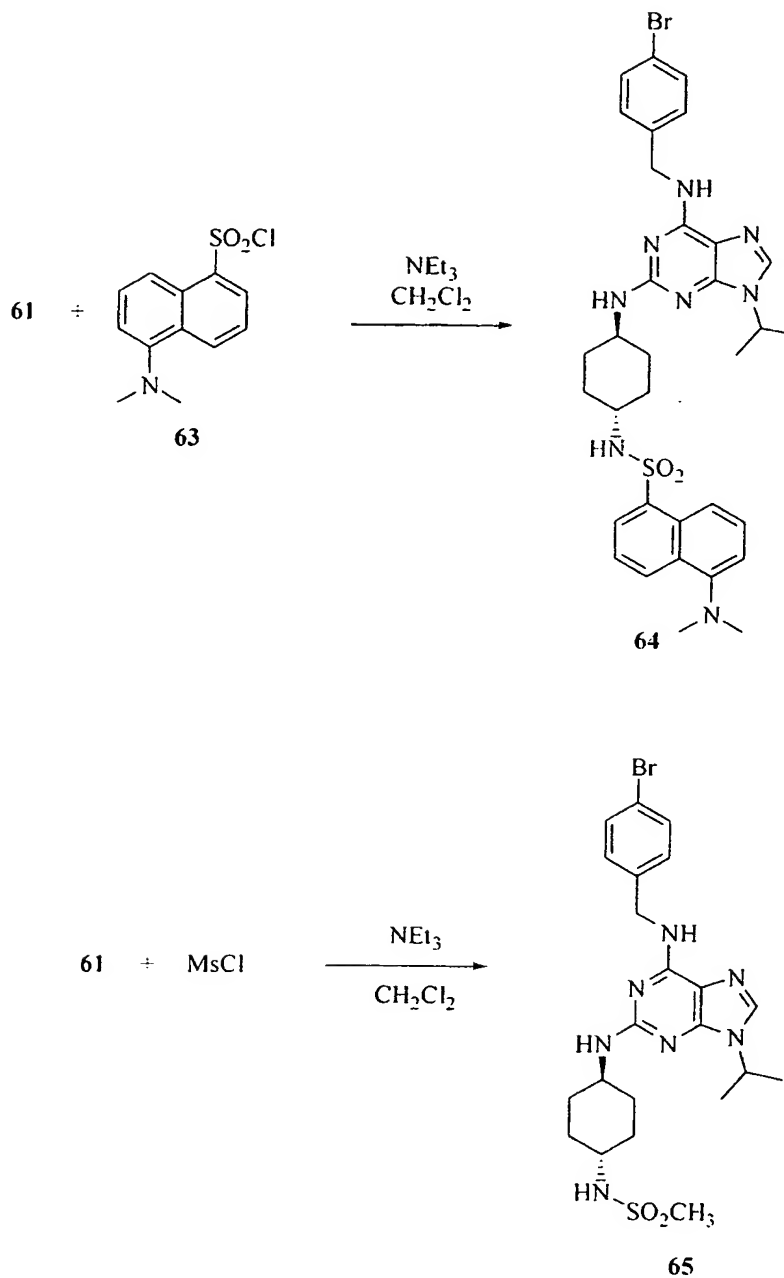
The syntheses of compounds **61**, and **62** are shown below in Scheme XIX.

Scheme XIX



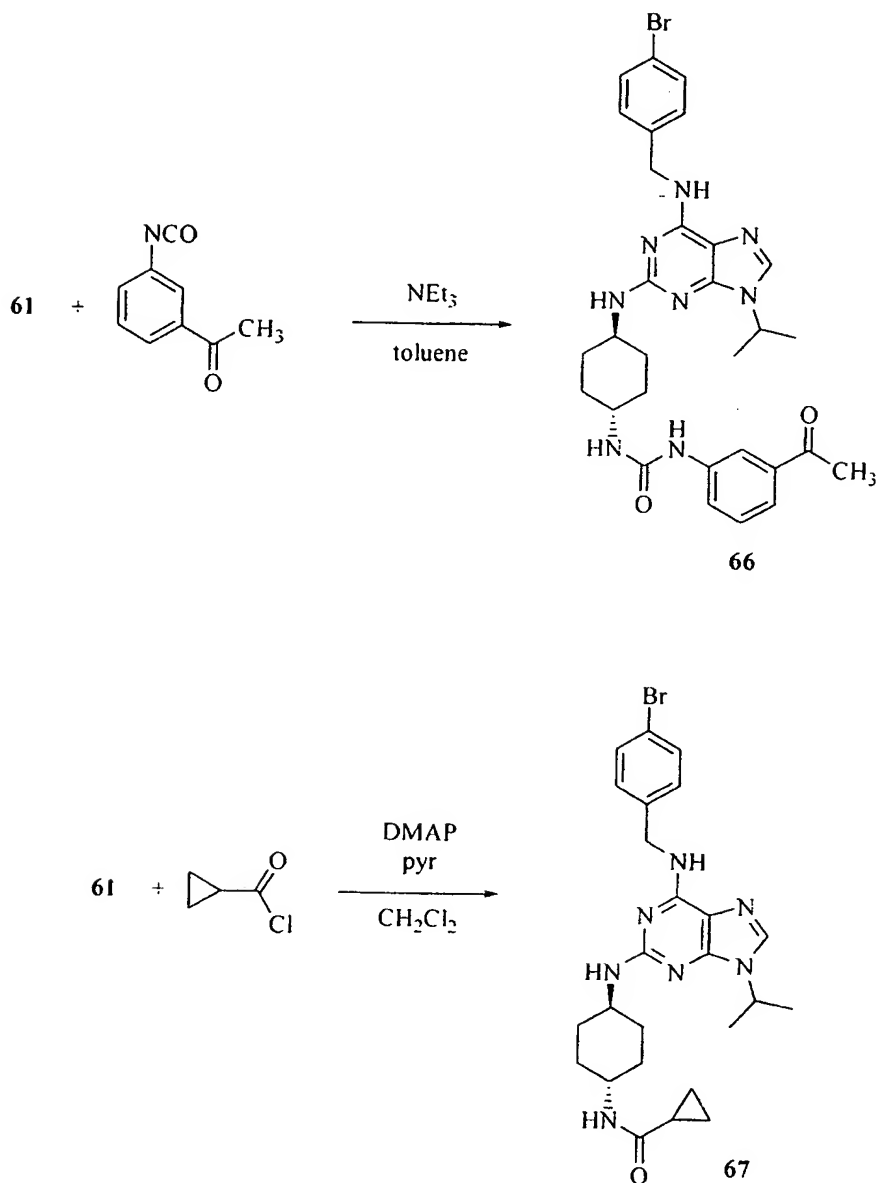
The syntheses of compounds 64. and 65 are shown below in Scheme XX.

Scheme XX



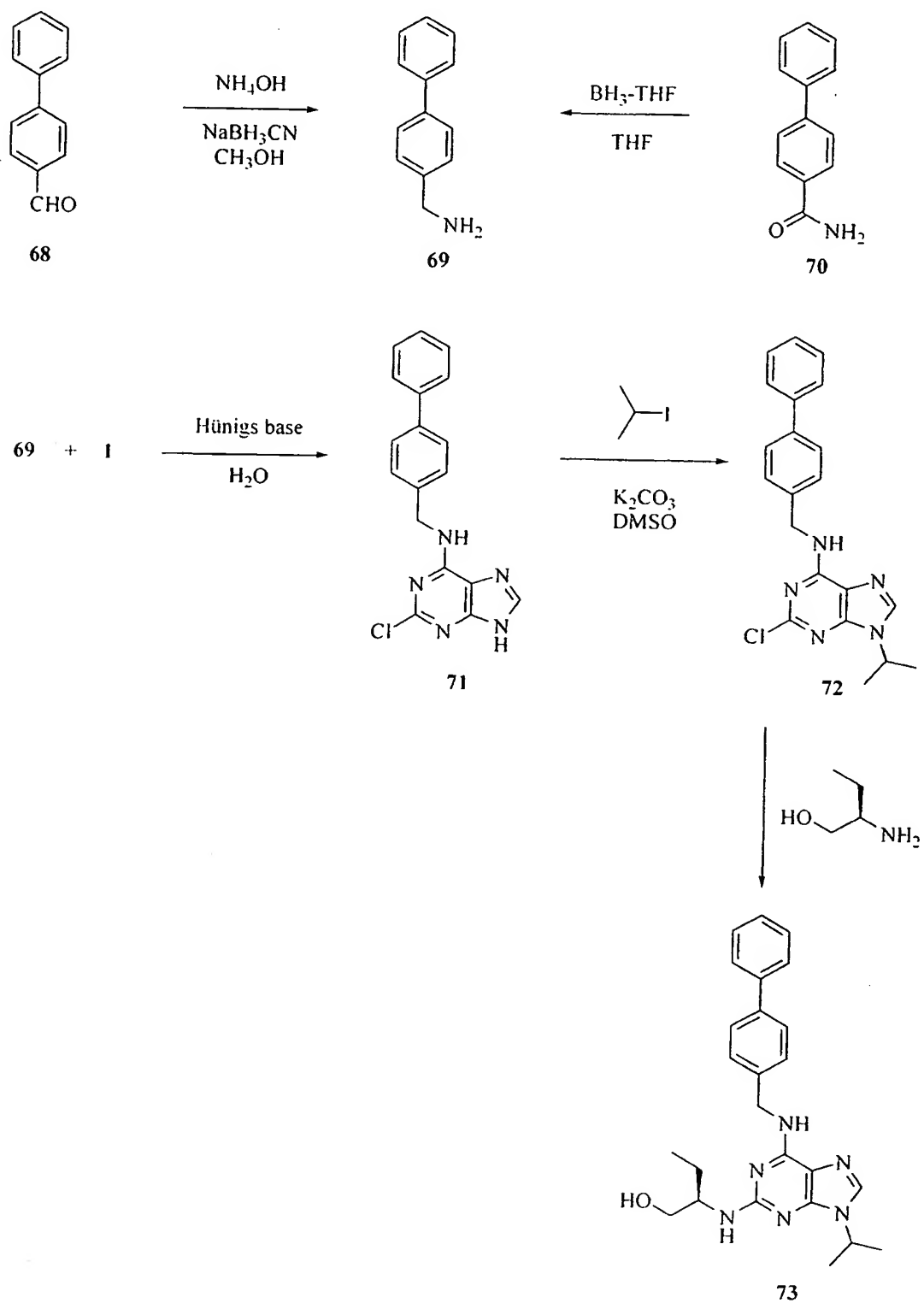
The syntheses of compounds 66. and 67 are shown below in Scheme XXI.

Scheme XXI



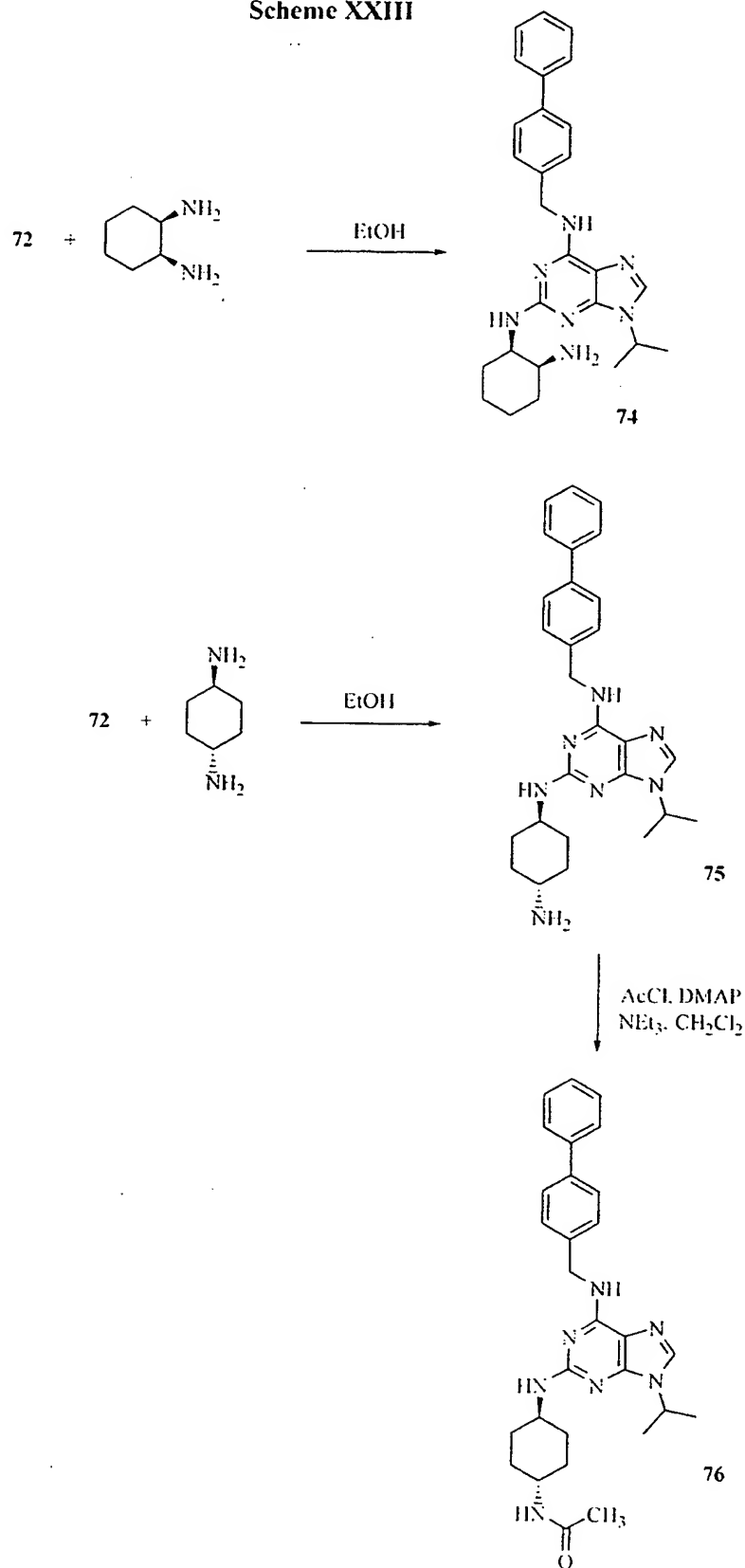
The synthesis of compound 73 is shown below in Scheme XXII.

Scheme XXII



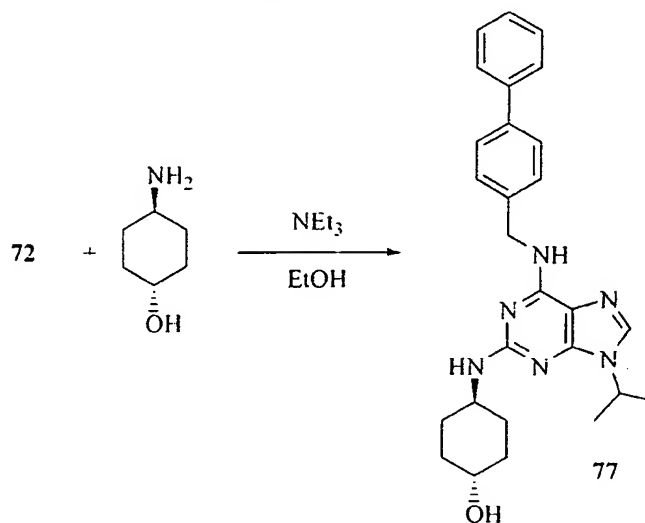
The syntheses of compounds **74**, **75**, and **76** are shown below in Scheme XXIII.

Scheme XXIII



The synthesis of compound **77** is shown below in Scheme XXIV.

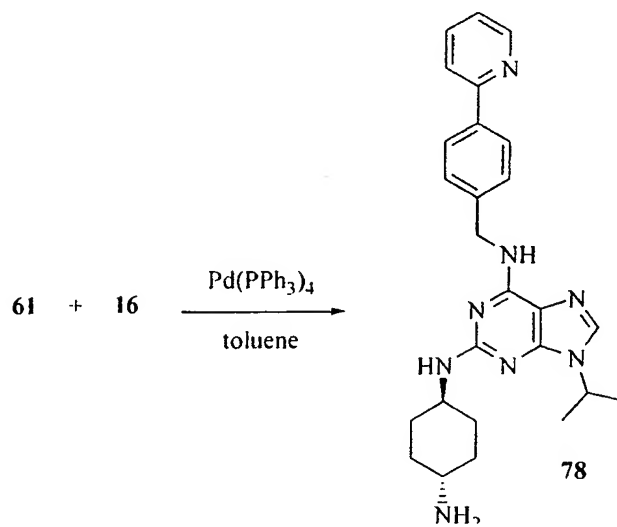
Scheme XXIV



5

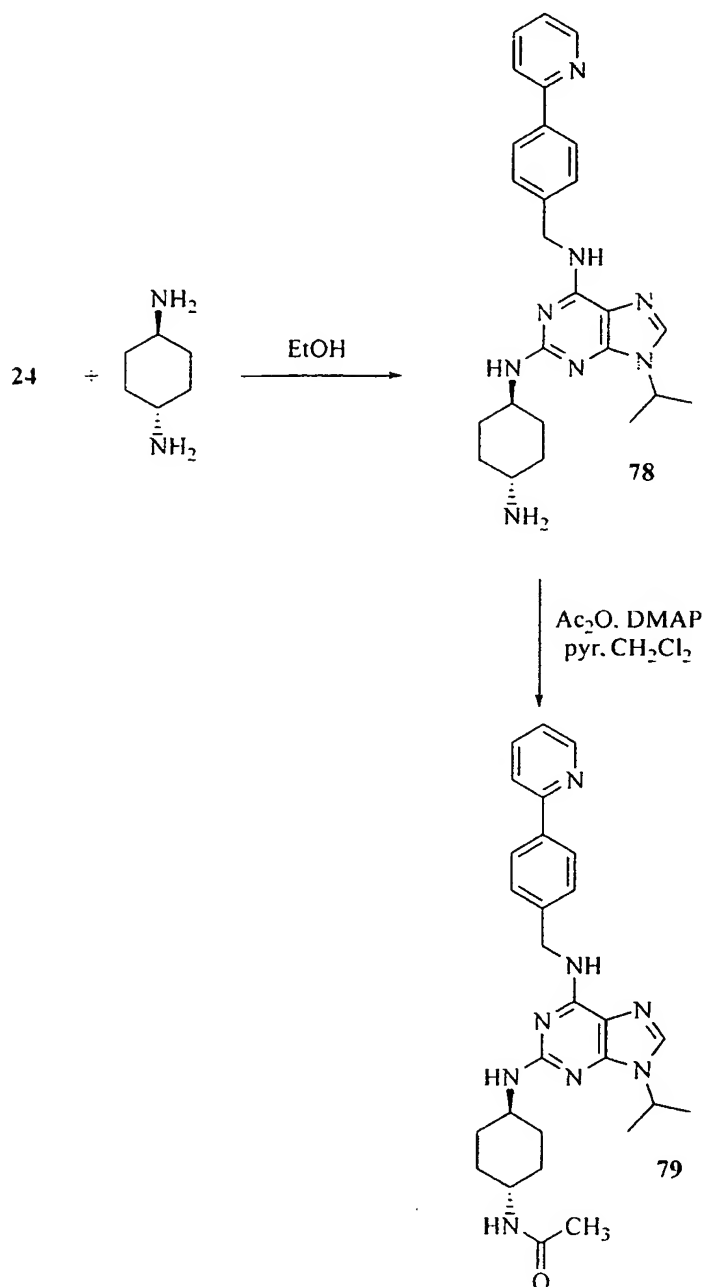
The synthesis of compound **78** is shown below in Scheme XXV.

Scheme XXV



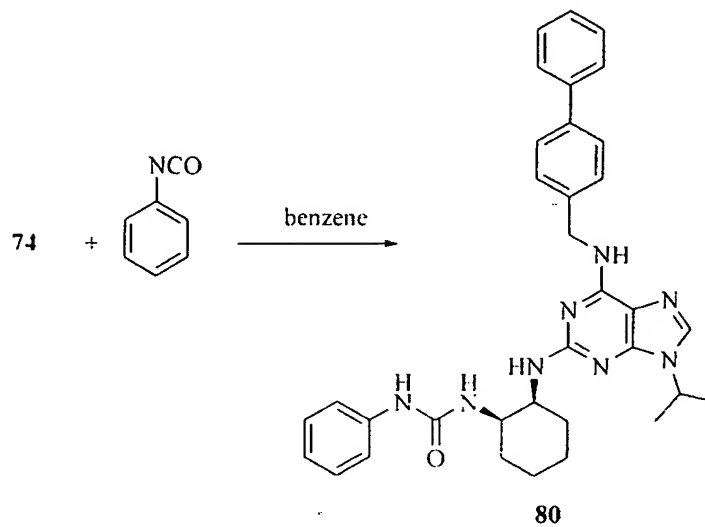
An alternative synthesis of compound 78, and the synthesis of compound 79 are shown below in Scheme XXVI.

Scheme XXVI



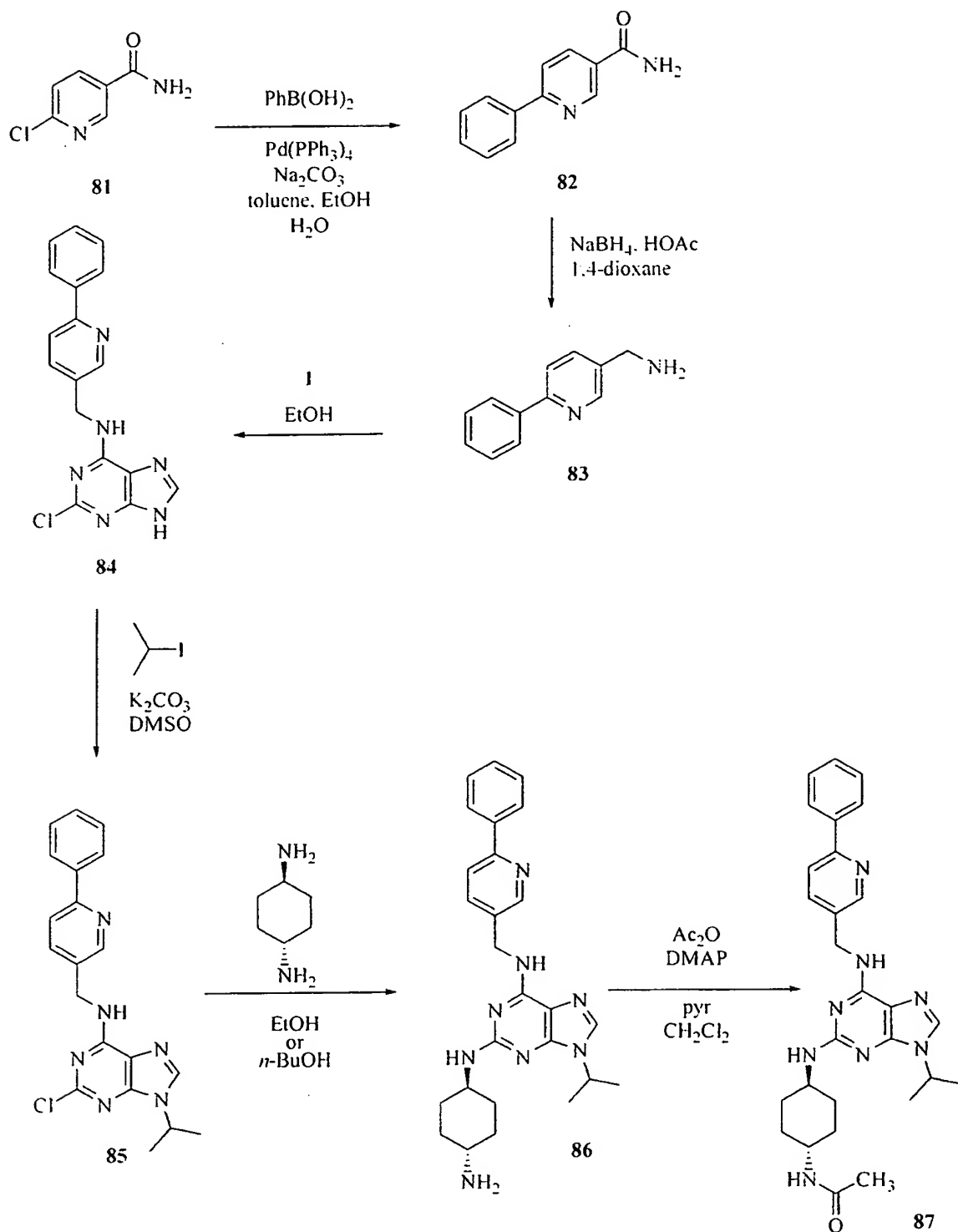
The synthesis of compound **80** is shown below in Scheme XXVII.

Scheme XXVII



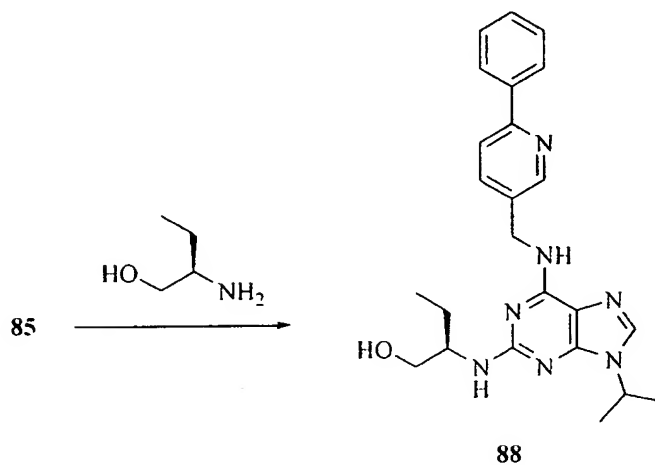
The syntheses of compounds **86**. and **87** are shown below in Scheme XXVIII.

Scheme XXVIII



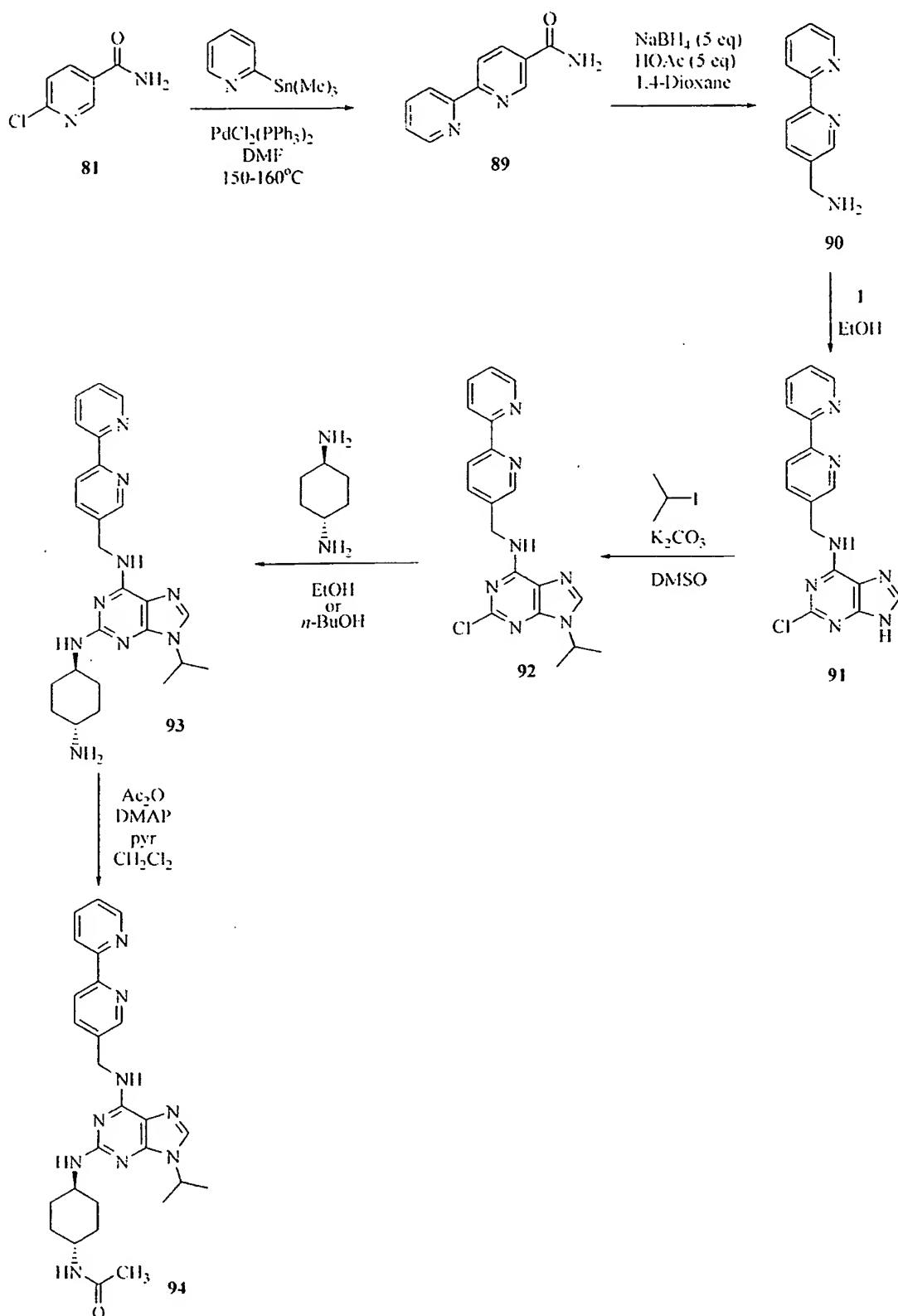
The synthesis of compound **88** is shown below in Scheme XXIX.

Scheme XXIX



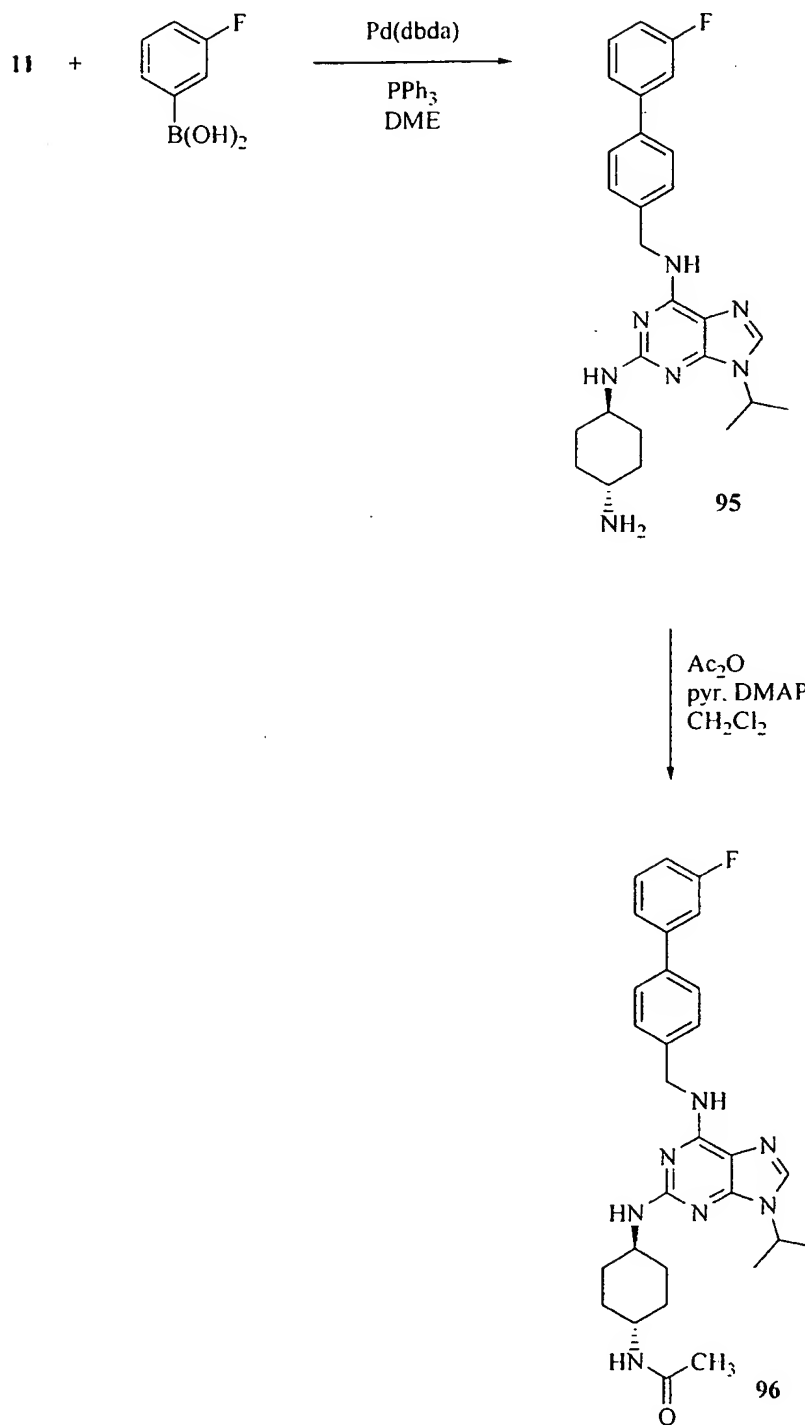
The syntheses of compounds **93**, and **94** are shown below in Scheme XXX.

Scheme XXX



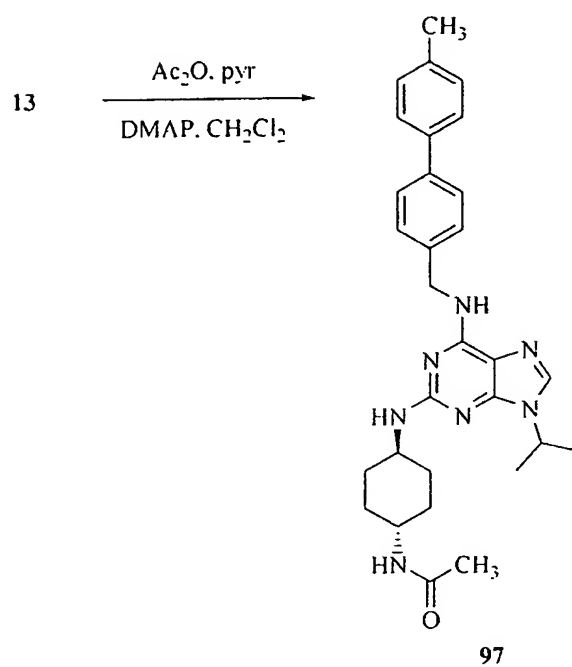
The syntheses of compounds **95** and **96** are shown below in Scheme XXXI.

Scheme XXXI



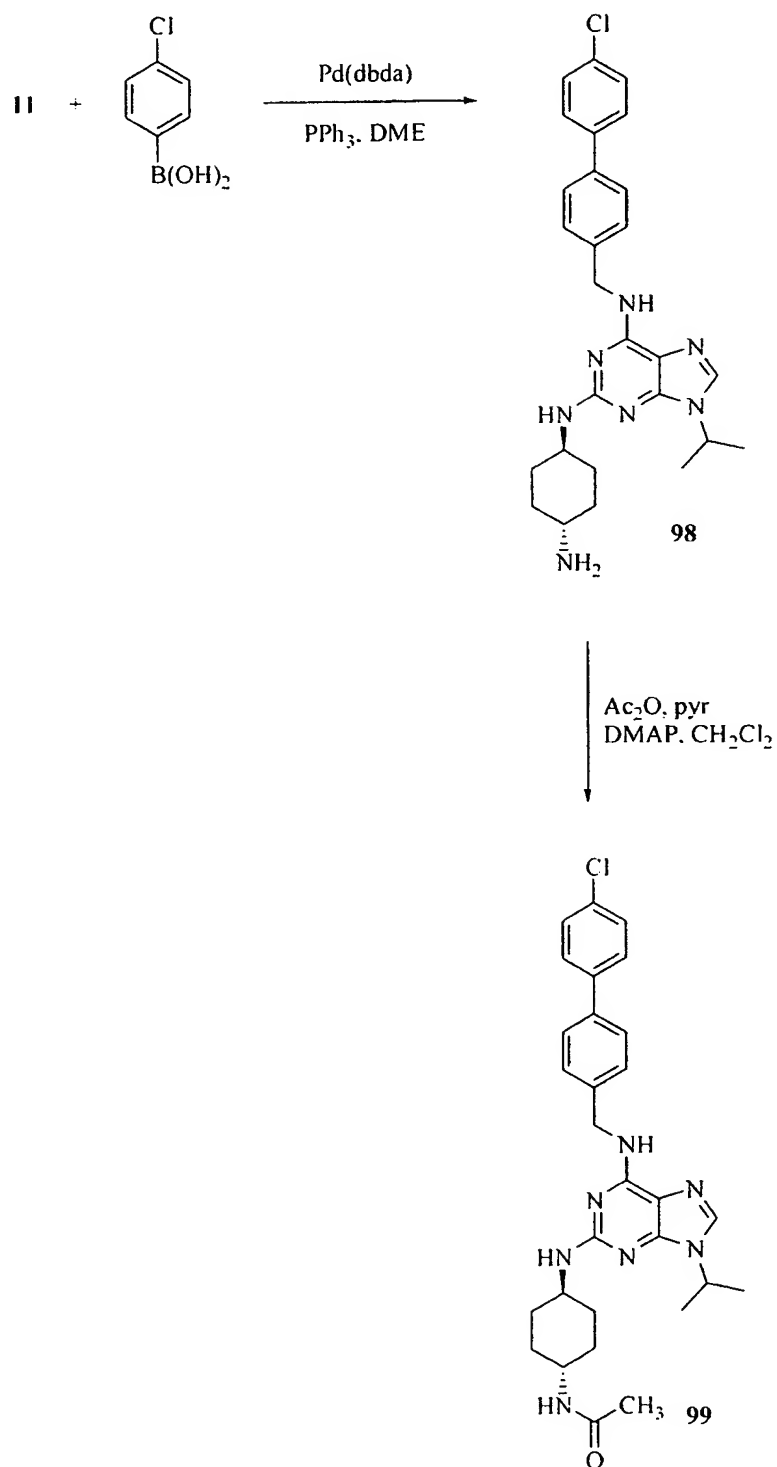
The synthesis of compound **97** is shown below in Scheme XXXII.

Scheme XXXII



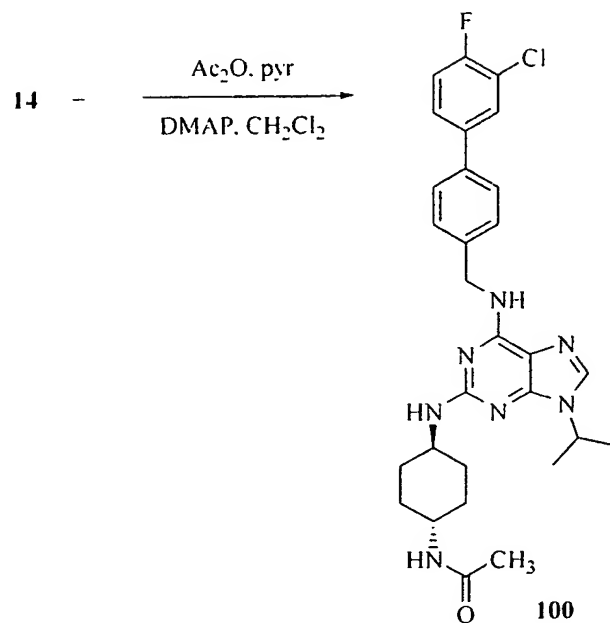
The syntheses of compounds **98**, and **99** are shown below in Scheme XXXIII.

Scheme XXXIII



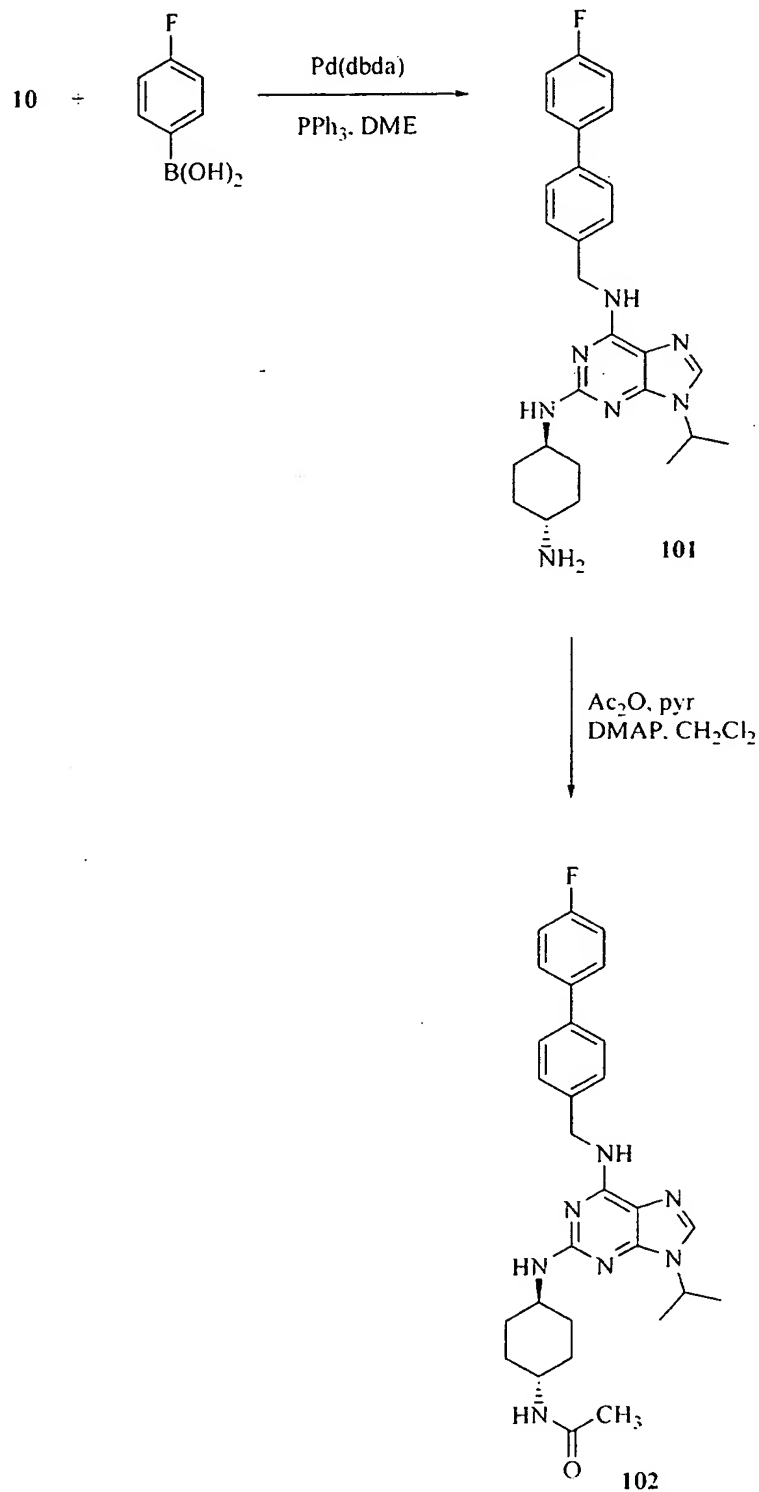
The synthesis of compound **100** is shown below in Scheme XXXIV.

Scheme XXXIV



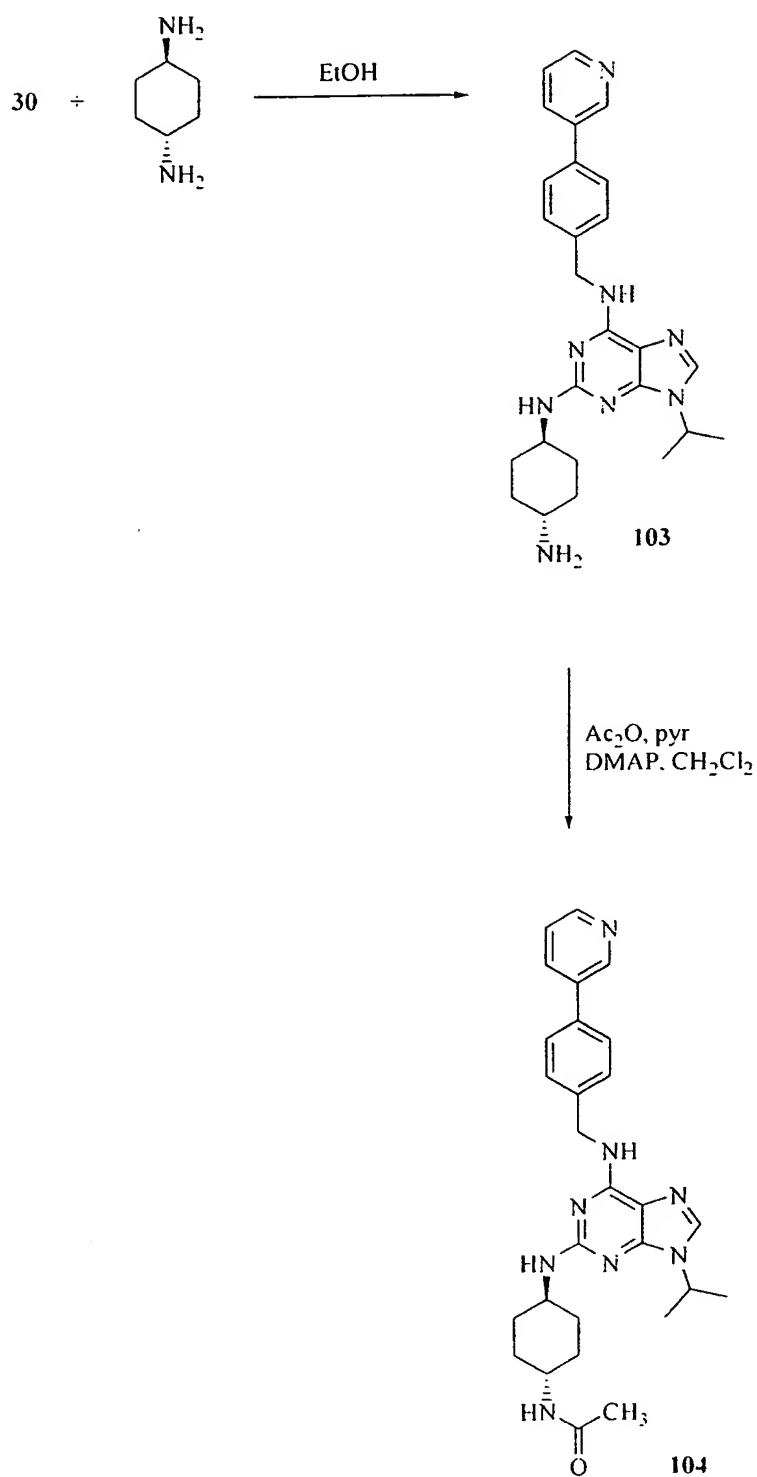
The syntheses of compounds **101**, and **102** are shown below in Scheme XXXV.

Scheme XXXV



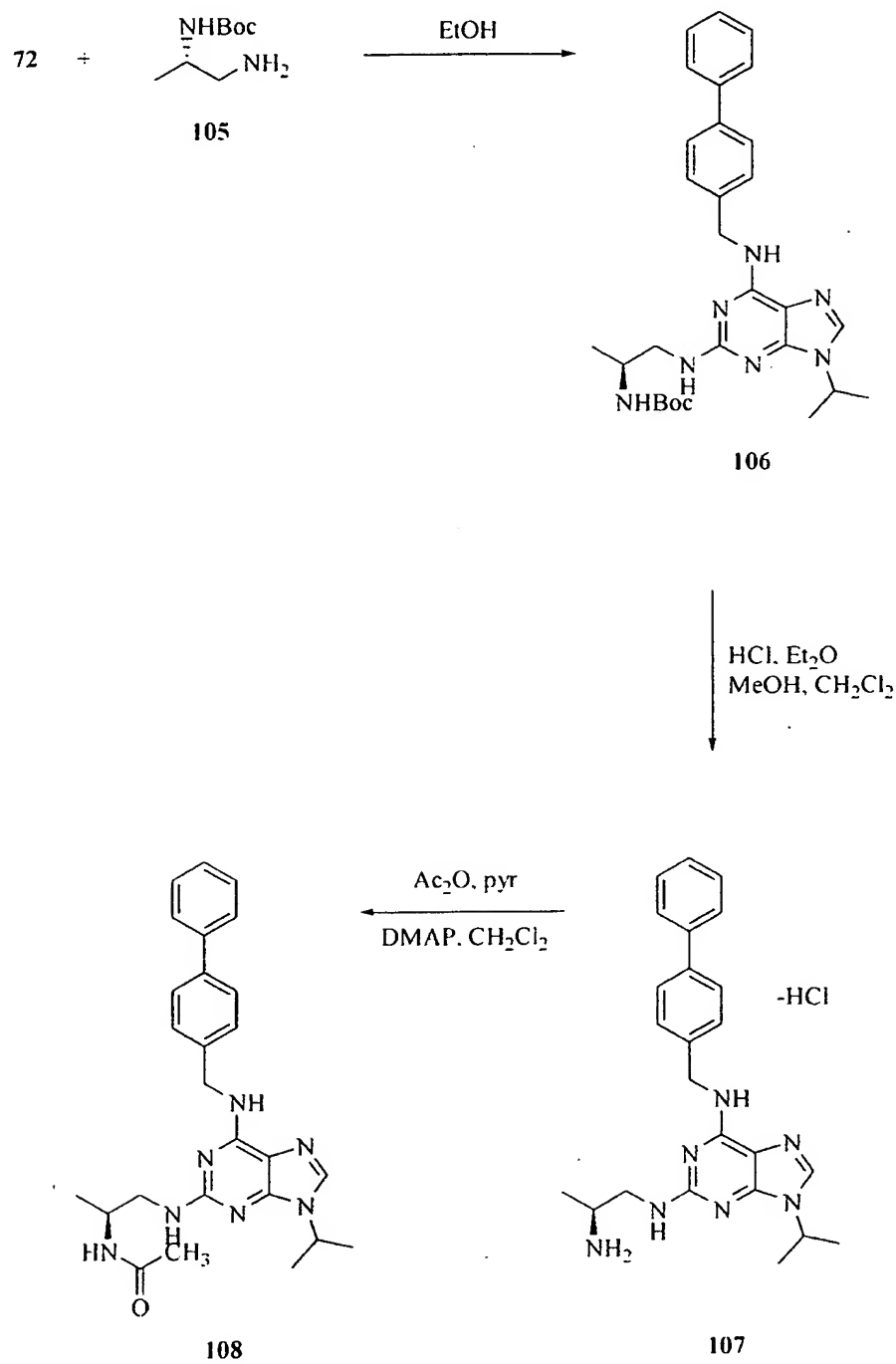
The syntheses of compounds **103**, and **104** are shown below in Scheme XXXVI.

Scheme XXXVI



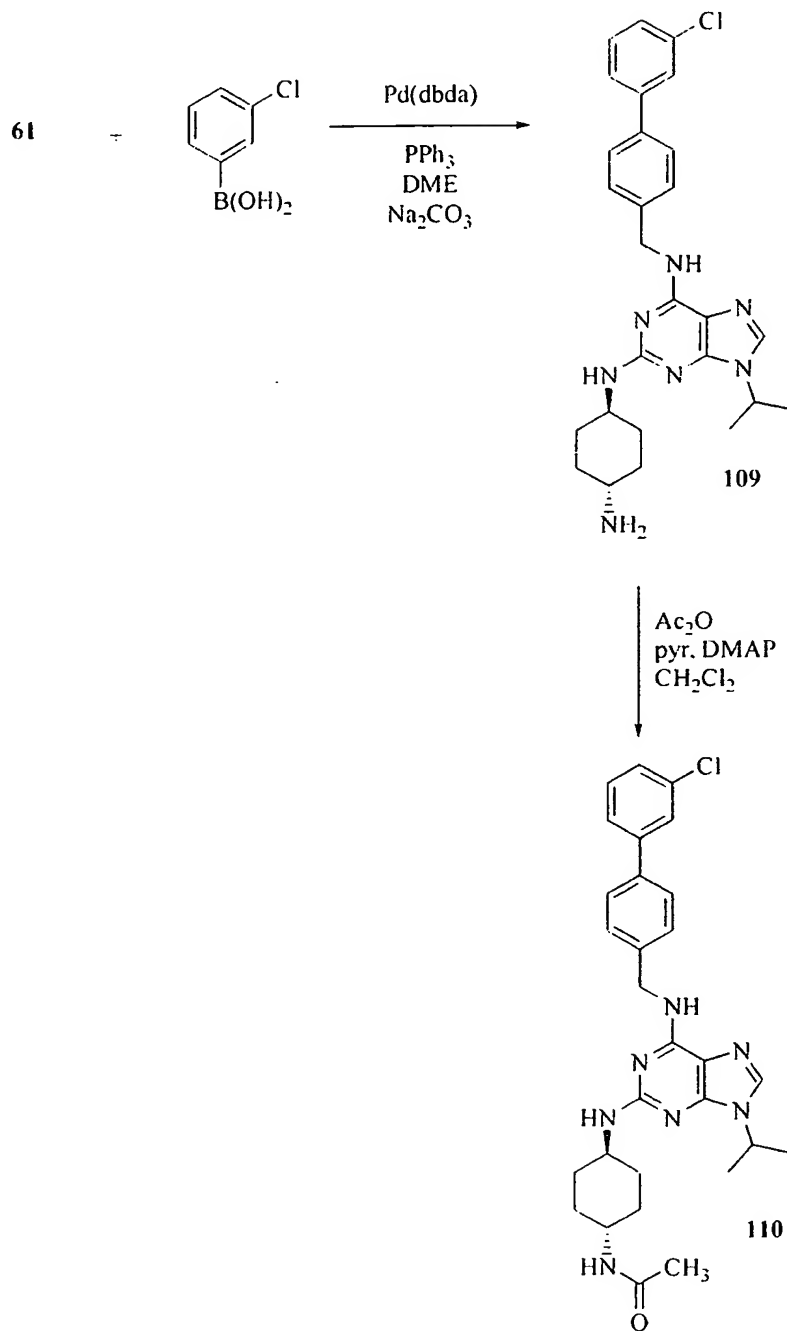
The syntheses of compounds **106**, **107**, and **108** are shown below in Scheme XXXVII.

Scheme XXXVII



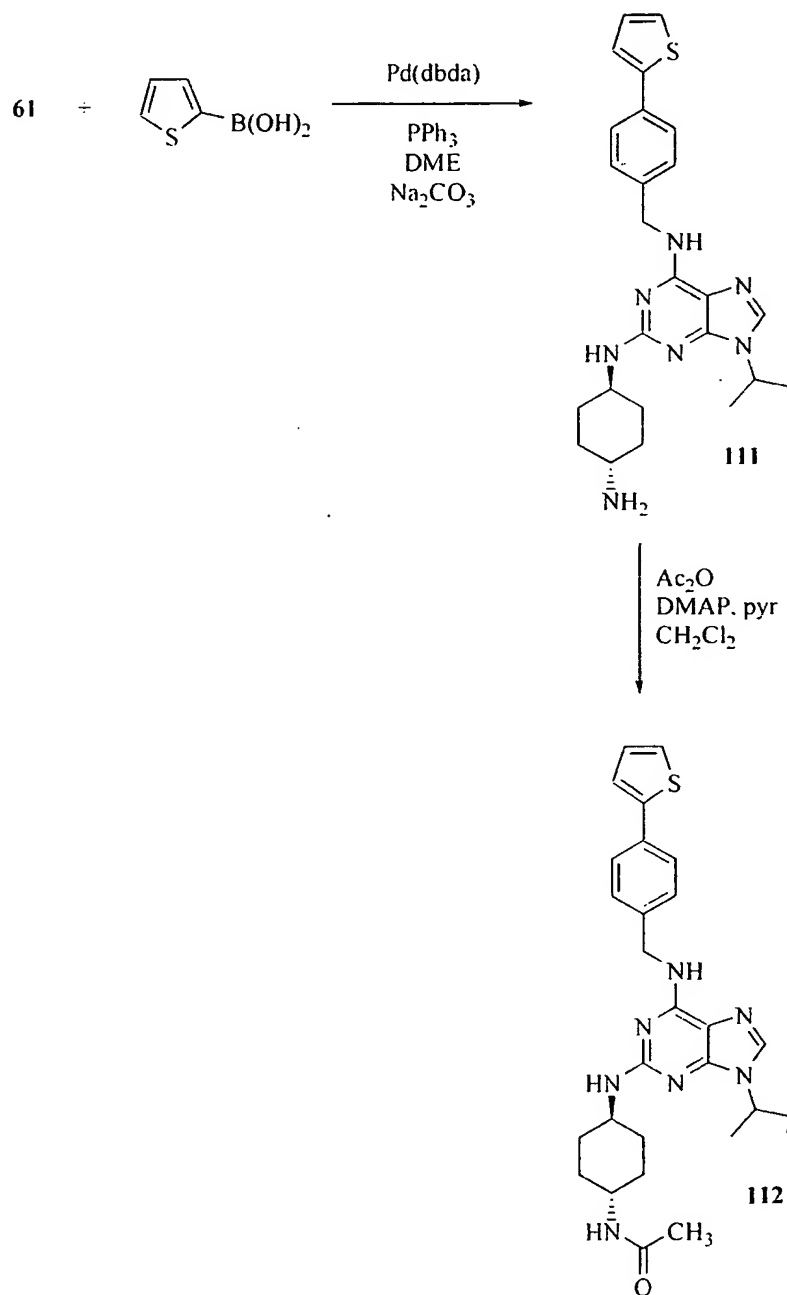
The syntheses of compounds **109**, and **110** are shown below in Scheme XXXVIII.

Scheme XXXVIII



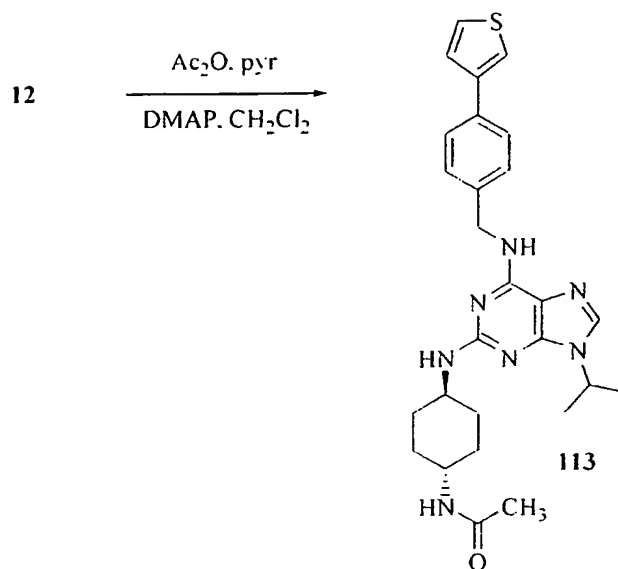
The syntheses of compounds **111**, and **112** are shown below in Scheme XXXIX.

Scheme XXXIX

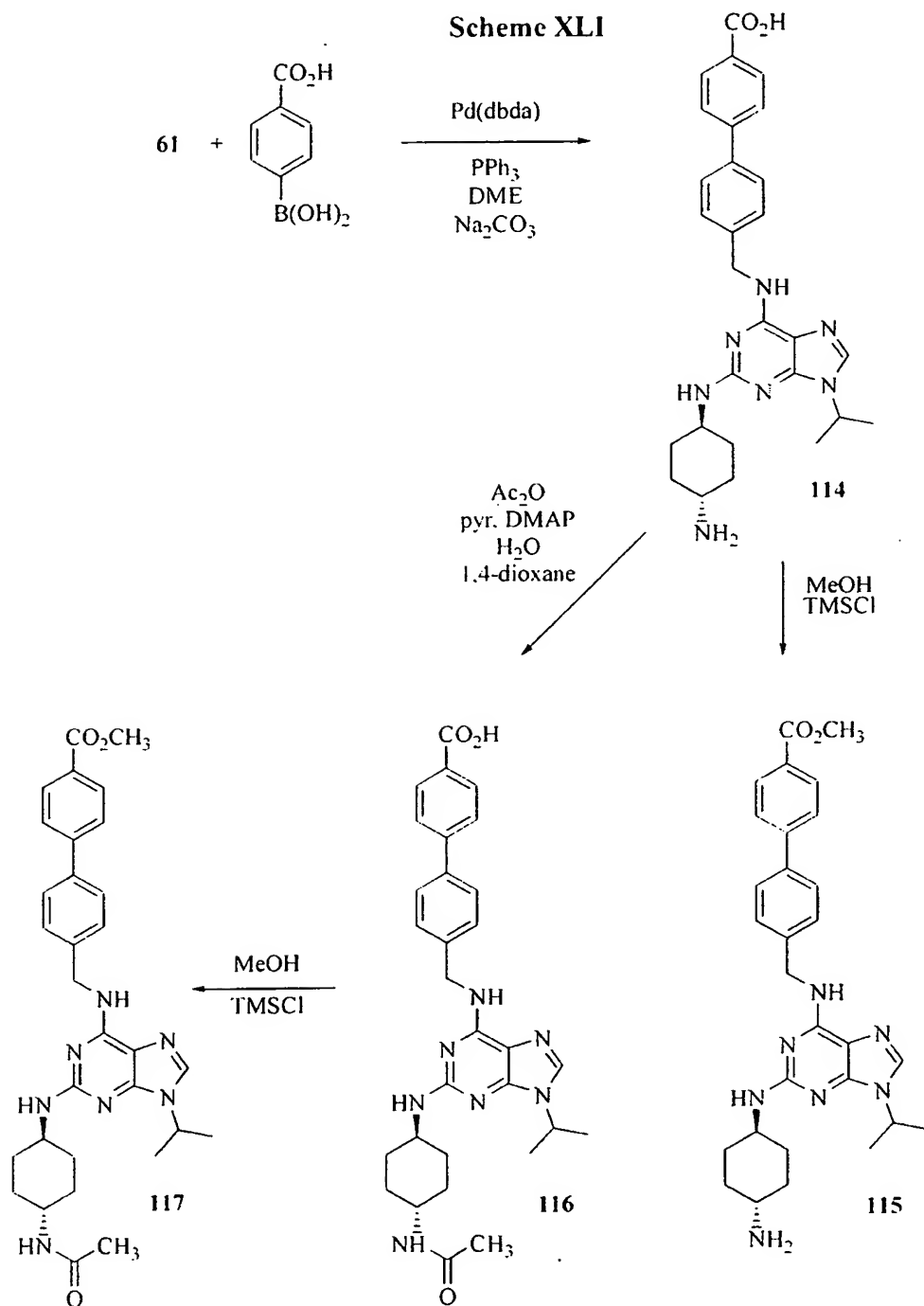


The synthesis of compound **113** is shown below in Scheme XL.

Scheme XL

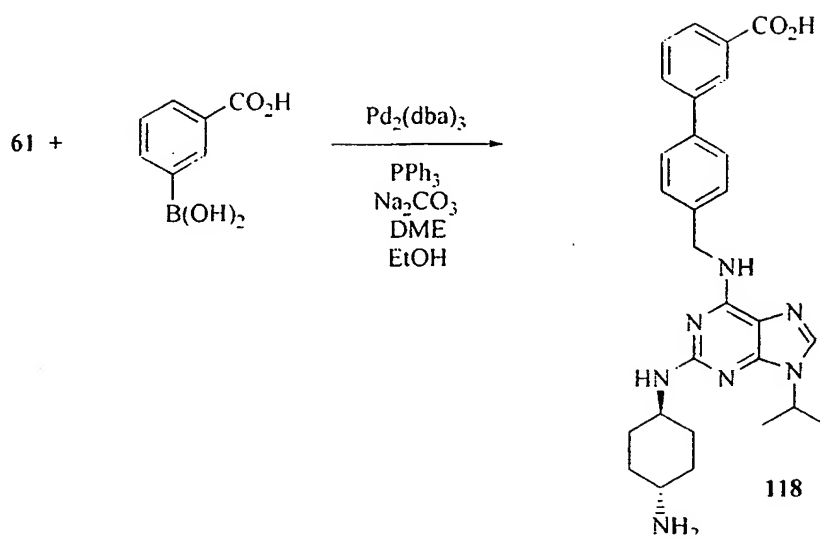


The syntheses of compounds **114**, **115**, **116**, and **117** are shown below in Scheme XLI.



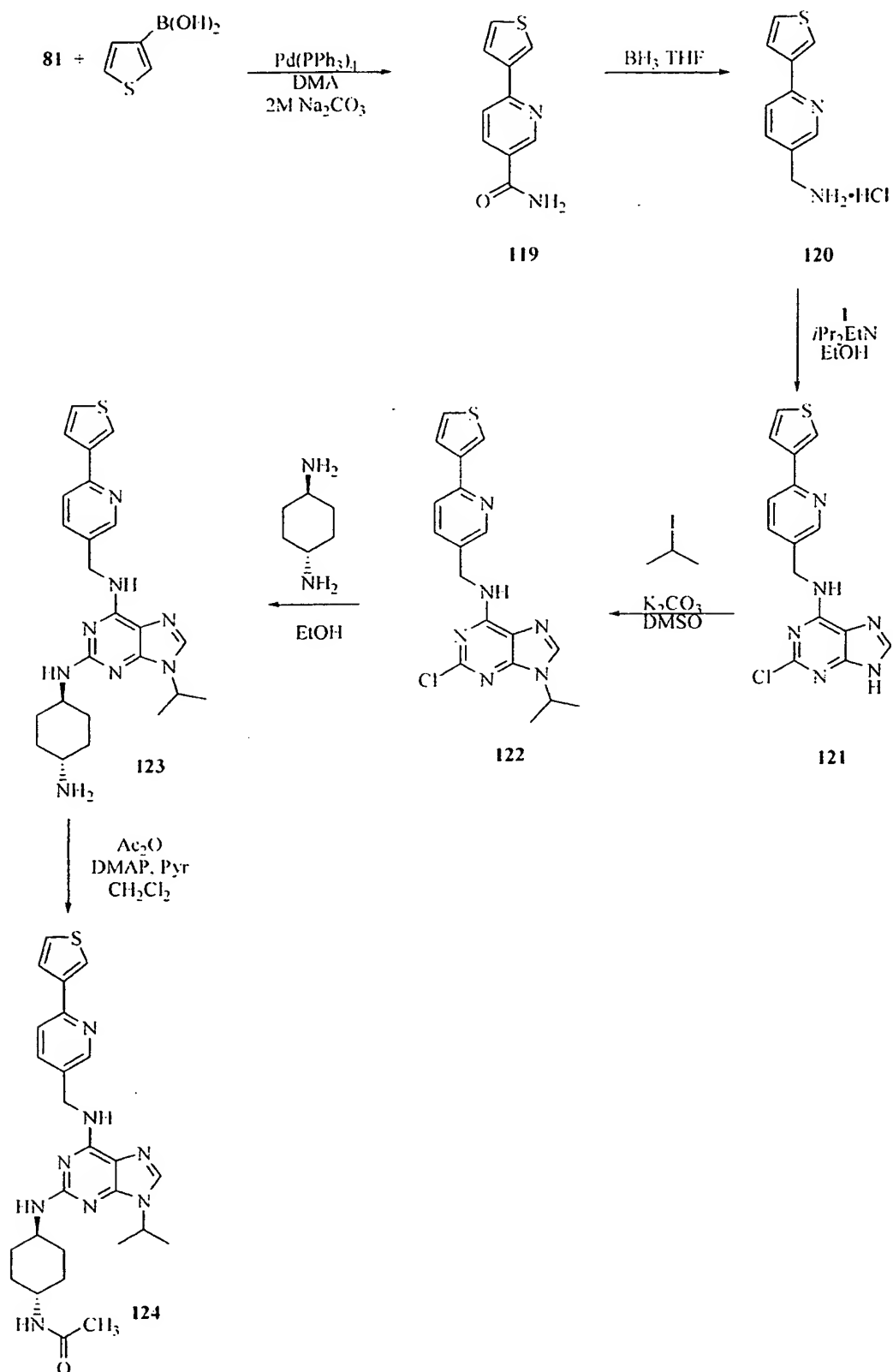
The synthesis of compound **118** is shown below in Scheme XLII.

Scheme XLII



The syntheses of compounds **123** and **124** are shown below in Scheme XLIII.

Scheme XLIII



EXAMPLES

Proton NMR spectra were obtained on a Bruker AC 300 spectrometer at 300 MHz or a Bruker 500 MHz spectrometer and were referenced to tetramethylsilane as an internal standard. The IR spectrometer used was a single beam Perkin-Elmer Spectrum 1000 FT-IR. All IR spectra obtained were prepared in a pressed disc of KBr. All IR spectra obtained were acquired with a total of 4 accumulations at a resolution of 4.00 cm⁻¹. Melting points were obtained on a Mel-Temp II apparatus and are uncorrected. Mass spectra were obtained on either a Shimadzu QP-5000 or a PE Sciex API 150 Mass Spectrometer.

Example 1 - Preparation of Compound 2

To the starting material 1 (1.0 g, 5.29 mmol) was added 4-bromobenzylamine (2.53 g, 11.4 mmol), and EtOH (11 mL). The mixture was stirred and heated at 50 °C in a round-bottomed flask and then H₂O (1 mL) and EtOH (10 mL) were added to dissolve the solids. The mixture was refluxed for 1 h. Hünig's base (3.68 mL, 21.2 mmol) was added and refluxed overnight, during which time a precipitate formed. The solution was filtered to provide a light yellow solid. The solid was dried *in vacuo* (1.08 g, 60%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.75 (bs, 1 H), 8.15 (s, 1 H), 7.52 (d, 2 H), 7.30 (d, 2 H), 4.63 (bs, 2 H); CI MS *m/z* = 340 [C₁₂H₉BrClN₅+H]⁺.

Example 2 - Preparation of Compound 3

To the starting material 2 (1.08 g, 3.19 mmol) was added DMSO (11 mL), K₂CO₃ (2.20 g, 15.95 mmol), and 2-iodopropane (1 mL, 9.57 mmol). The solution was stirred overnight then poured into H₂O (75 mL) and stirred. Additional H₂O (25-50 mL) was added to the mixture to form a yellow solid. The stirring was continued at 0 °C. The solid was filtered *in vacuo*. The crude product was purified by silica gel chromatography to provide 3 (0.66 g, 50%) as a white solid: mp 136-140 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (s, 1 H), 7.49 (d, 2 H), 7.28 (d, 2 H), 6.12 (bs, 1 H), 4.90-4.70 (m, 3 H), 1.61 (d, 6 H).

Example 3 - Preparation of Compound 4

To starting material **3** (1.44 g, 3.78 mmol) was added 2-amino-1-butanol (5.06 g, 56.7 mmol) and ethanol (5 mL) and the mixture was heated in a sealed tube in an oil bath at 150-160 °C for 48 h. The cooled solution was transferred to a round-bottomed flask and the ethanol was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel to give **4** (0.90 g, 55%):
¹H NMR (300 MHz, CDCl₃) δ 7.44-7.41 (m, 3 H), 7.23 (d, 2 H), 6.22 (s, 1 H), 5.06 (s, 1 H), 4.90 (d, 1 H), 4.78-4.68 (m, 2 H), 4.65-4.55 (m, 1 H), 3.91-3.80 (m, 2 H), 3.66-3.60 (m, 1 H), 1.66-1.47 (m, 8 H), 1.04-0.99 (t, 3 H).

Example 4 - Preparation of Compound 5

To starting material **4** (0.13 g, 0.29 mmol) was added 3-acetamidophenylboronic acid (0.21 g, 1.19 mmol) and Pd(PPh₃)₄ (0.08 g, 0.07 mmol), Na₂CO₃ (2M, 0.60 mL), and toluene (5 mL). The solution was degassed with argon for 10 min then heated at 130 °C for 6 h. The cooled solution was diluted with water and then extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated to yield a viscous orange oil. The oil was purified by flash column chromatography on silica gel and then the product crystallized upon standing to give **5** (0.06 g, 41%) as a pale yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.01-7.21 (m, 9 H), 6.48 (s, 1 H), 4.97 (d, 1 H), 4.82-4.70 (m, 2 H), 4.65-4.53 (m, 1 H), 3.98-3.25 (m, 2 H), 3.20-3.05 (m, 1 H), 2.20 (s, 3 H), 1.69-1.45 (m, 8 H), 1.07-0.98 (t, 3 H).

Example 5 - Preparation of Compound 7

To 4-iodobenzoic acid (52.2 g, 0.21 mol) was added CH₂Cl₂ (500 mL) and DMF (2 drops) at room temperature. Oxalyl chloride (32 g, 0.25 mol) was added dropwise in 0.5 h and stirred for 2 d. The volatiles were removed *in vacuo* to a volume of 150 mL to give the acid chloride and CH₂Cl₂. To a mixture of ice (500 mL) and NH₄OH (29%: 100 mL) was added the CH₂Cl₂ solution during 15 min. The resulting solids were collected, washed with CH₂Cl₂, and dried *in vacuo*. The solids

were slurried in H₂O for 1 h. The solids were collected by filtration, washed in water and acetone, and dried *in vacuo* to give **7** (48 g; 92%): mp 213-216 °C.

Example 6 - Preparation of Compound 8

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To a suspension of **7** (11 g, 45 mmol) in THF (50 mL) was added BH₃-THF (1M, 22.5 mL, 22.5 mmol). The resulting solution was heated under reflux overnight. The reaction was cooled in an ice bath and MeOH-HCl (60 mL) was slowly added dropwise. The resulting precipitate was filtered and dried to give **8** (10.8 g, 88%) as a white solid: mp 256-262 °C dec.: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.55 (bs, 3 H), 7.79 (d, 2 H), 7.32 (d, 2 H), 3.98 (s, 2 H).

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Example 7 - Preparation of Compound 9

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To compound **1** (7.63 g, 40.4 mmol) was added compound **8** (10.8 g, 40.4 mmol), water (123 mL), and Hünig's base (14 mL, 81 mmol). The mixture was heated to reflux for 5 h and stirred overnight at room temperature to give a pale yellow solution. An additional quantity of water (150 mL) was added, refluxed for 3 h, then cooled overnight. A pale yellow solid was formed which was filtered, washed with water, rinsed with EtOH (2 x), and dried *in vacuo* to give yield **9** (13.3 g, 80%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (bs, 1 H), 8.28 (s, 1 H), 7.68 (d, 2 H), 7.50 (d, 2 H), 5.08 (bs, 1 H), 4.50 (d, 2 H).

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Example 8 - Preparation of Compound 10

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To compound **9** (12.2 g, 31.7 mmol) was added K₂CO₃ (35 g, 0.25 mol), 2-iodopropane (13 g, 0.13 mol) and DMSO (210 mL). The reaction mixture was stirred under N₂ at room temperature overnight, then poured into H₂O (1.5 L) and stirred for 2 d. The precipitate was collected as an off-white solid and washed with Et₂O. The aqueous layer was extracted with EtOAc (2 x) and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and evaporated to give an off-white foam (6.4 g). This off-white foam was combined with the precipitate and washed with Et₂O to give **10** (11.0 g): ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.91 (m, 1

30

H). 8.38 (s, 1 H), 7.74 (d, 2 H), 7.21 (d, 2 H), 5.11 (bs, 1 H), 4.68 (m, 1 H), 4.60 (d, 2 H), 1.48 (d, 6 H).

Example 9 - Preparation of Compound 11

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Compound **10** (1.52 g, 3.55 mmol), *trans*-1,4-diaminocyclohexane (6.35 g, 55.60 mmol), and EtOH (18 mL) were placed in a sealed tube. The reaction mixture was heated at 120-190 °C for 24 h. The reaction was then allowed to cool to room temperature. The reaction mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography, and dried *in vacuo* for 16 h to yield **11** (1.60 g, 89%) as a yellow sticky oil: ¹H NMR (300 MHz, CDCl₃) δ 7.62 (d, 2 H), 7.44 (s, 1 H), 7.08 (d, 2 H), 6.14 (br, 1 H), 4.75-4.63 (m, 2 H), 4.63-4.54 (m, 2 H), 3.75-3.63 (m, 1 H), 2.72-2.57 (m, 2 H), 2.18-2.00 (m, 2 H), 2.00-1.75 (m, 4 H), 1.54 (d, 6 H), 1.39-1.00 (m, 3 H); API MS *m/z* = 506 [C₂₁H₂₈IN₇+H]⁺.

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Example 10 - Preparation of Compound 12

To compound **11** (0.133 g, 0.26 mmol) was added DME (2.5 mL) and 3-thiopheneboronic acid (0.12 g, 0.97 mmol) in a round-bottomed flask and equipped with a condenser purged with argon. To this was added DME (3 mL) followed by tris(dibenzylidoneacetone)dipalladium (0.01 g, 0.01 mmol) and PPh₃ (0.04 g, 0.15 mmol). Na₂CO₃ (2M, 0.6 mL) and DME (1 mL) was added to the reaction mixture and the reaction mixture was allowed to reflux for 18.5 h, then stirred at room temperature under argon for 46 h. The reaction mixture was diluted with H₂O and extracted with CH₂Cl₂. The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to yield **12** (0.050 g, 41%) as a tan solid: ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.50 (m, 4 H), 7.44-7.35 (m, 3 H), 6.02 (br, 1 H), 4.78 (d, 2 H), 4.69-4.54 (m, 2 H), 3.75 (br, 1 H), 2.69 (br, 1 H), 2.15 (br, 2 H), 1.88 (br, 3 H), 1.54 (d, 7 H), 1.33-0.97 (m, 4 H); API MS *m/z* = 462 [C₂₅H₃₁N₇S+H]⁺.

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Example 11 - Preparation of Compound 13

DME (3 mL), tris(dibenzylideneacetone)dipalladium (0.01 g, 0.01 mmol), and PPh₃ (0.04 g, 0.15 mmol) were placed in a round-bottomed flask fitted with a condenser and maintained under argon. Compound **11** (0.13 g, 0.26 mmol), and 4-methylbenzeneboronic acid (0.13 g, 0.98 mmol) dissolved in Na₂CO₃ (2M, 0.6 mL) and DME (1 mL) were added to the reaction mixture. The reaction mixture was refluxed for 19.5 h and stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, and evaporated. The crude product was purified by column chromatography and dried *in vacuo* for 22 h to yield the desired product **13** (54 mg, 44%) as an off-white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.41 (m, 7 H), 7.23 (s, 1 H), 5.92 (br, 1 H), 4.83 (d, 2 H), 4.74-4.58 (m, 2 H), 3.77 (br, 1 H), 2.70 (br, 1 H), 2.40 (s, 3 H), 2.16 (d, 3 H), 1.88 (d, 3 H), 1.55 (d, 7 H), 1.33-0.97 (m, 4 H); API MS *m/z* = 470 [C₂₈H₃₅N₇+H]⁺.

Example 12 - Preparation of Compound 14

DME (3 mL), tris(dibenzylideneacetone)dipalladium (0.01 g, 0.01 mmol), and PPh₃ (0.04 g, 0.15 mmol) were placed in a round-bottomed flask with a condenser under argon. Compound **11** (0.13 g, 0.25 mmol) and 3-chloro-4-fluoroboronic acid (0.15 g, 0.88 mmol) were dissolved in Na₂CO₃ (2M, 0.6 mL) and DME (1 mL) were added to the reaction mixture, refluxed for 19 h then stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, and evaporated. The crude product was purified by repeated column chromatography to yield **14** (0.019 g, 15%): ¹H NMR (300 MHz, CDCl₃) δ 7.59-7.53 (m, 1 H), 7.47-7.35 (m, 4 H), 7.26-7.14 (m, 3 H), 5.81 (br, 1 H), 4.81 (d, 2 H), 4.72-4.54 (m, 2 H), 3.72 (br, 1 H), 2.69 (br, 1 H), 2.21-2.03 (m, 3 H), 1.94-1.78 (m, 3 H), 1.54 (d, 6 H), 1.33-1.12 (m, 4 H); API MS *m/z* = 508 [C₂₇H₃₁ClFN₇+H]⁺.

Example 13 - Preparation of Compound 16

A solution of **15** (2.5 g, 15.8 mmol) and ether was cooled to -78 °C. In a separate flask, *n*-BuLi (15.8 mmol) was also cooled to -78 °C. The solution of **15** was added to the *n*-BuLi solution *via* cannula to give a dark red solution. The reaction mixture was stirred for 5 min prior to the rapid addition of (*n*-Bu)₃SnCl (6.2 g, 19 mmol). The resulting bright yellow solution was stirred at -78 °C for 2 h, allowed to warm to room temperature, and stirred for another 10 min. The solution was then diluted with H₂O (80 mL) and extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by column chromatography gave the product **16** (4.89 g, 84%) as a pale yellow liquid: ¹H NMR (300 MHz, CDCl₃) δ 8.72 (d, 1 H), 7.48-7.46 (m, 1 H), 7.40-7.38 (m, 1 H), 7.11-7.09 (m, 1 H), 1.61-1.50 (m, 6 H), 1.38-1.26 (m, 6 H), 1.14-1.09 (m, 6 H), 0.97-0.77 (t, 9 H).

Example 14 - Preparation of Compound 17

To compound **16** (0.18 g, 0.48 mmol) was added compound **4** (0.14 g, 0.33 mmol), Pd(PPh₃)₄ (0.05 g, 0.49 mmol), and toluene (10 mL) in a sealed tube under an argon atmosphere. The solution was degassed with argon and heated at 135 °C in an oil bath for 3 h. The solution was cooled to room temperature, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (3 x 30 mL). The organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to give a light brown oil. The residue was purified by flash column chromatography using MeOH/CH₂Cl₂ (10%) to afford **17** as a white solid. The sample was dissolved into hexane/CH₂Cl₂/MeOH and then precipitated with diethyl ether, filtered, and rinsed several times with ether to provide **17** (30.3 mg): mp 95-100 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.68 (d, 1 H), 7.96 (d, 2 H), 7.77-7.69 (m, 2 H), 7.49-7.45 (m, 3 H), 7.24-7.20 (m, 1 H), 5.99 (s, 1 H), 5.11 (s, 1 H), 4.88-4.83 (m, 3 H), 4.65-4.56 (m, 1 H), 3.91-3.80 (m, 2 H), 3.65-3.60 (m, 1 H), 1.66-1.52 (m, 8 H), 1.05-0.99 (t, 3 H); IR (KBr) 3411, 2968, 1601, 1489 cm⁻¹; CI MS *m/z* = 432 [C₂₄H₂₉N₇+H]⁺.

Example 15 - Preparation of Compound 19

To a solution of *n*-BuLi (2.5M hexane solution, 10.9 mL, 27.4 mmol) in ethyl ether 28 mL at -78 °C was added 2-bromopyridine (4.33 g, 27.4 mmol) in ethyl ether (15 mL). After stirring for 30 min, a solution of trimethylstannylchloride (6.0 g, 30 mmol) in THF (10 mL) was added. Stirring was continued at -78 °C for 2 h and the mixture was then warmed up to room temperature and filtered. The precipitate was washed with ether and the combined ether filtrates were concentrated to give the crude product: ¹H NMR (500 Hz, CDCl₃) δ 8.69-8.68 (d, 1 H), 7.47-7.07 (m, 3 H), 0.30 (s, 9 H).

Example 16 - Preparation of Compound 21

A mixture of 4-bromobenzonitrile (1.68 g, 9.2 mmol), crude 2-trimethylstannylpyridine (3.33 g, 13.8 mmol), and PdCl₂(PPh₃)₂ (321 mg, 0.46 mmol) in DMF (25 mL) was heated at 150-155 °C in pressure tube for 24 h. The DMF was distilled off under reduced pressure and the residue was filtered through a short column of basic alumina and washed with ethyl acetate and then concentrated. Flash chromatography of the residue on silica gel gave the product (41%) as a white solid: mp 99-100 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.74 (dd, J₁ = 1 Hz, J₂ = 1.7 Hz, 1 H), 8.12 (d, J = 8.6 Hz, 2 H), 7.83-7.76 (m, 4 H), 7.32 (m, 1 H).

Example 17 - Preparation of Compound 22

To LiAlH₄ (8 mmol) in THF (25 mL) was added **21** (0.96 g, 5.3 mmol) in THF (15 mL) slowly while the flask was cooled with ice. The mixture was stirred at room temperature for 10-30 min then stirred at reflux for 4 h under nitrogen. The mixture was cooled in an ice bath and aqueous sodium hydroxide solution (0.5 mL, 10%) was added. The mixture was stirred until the residue became white and the solid was filtered and washed with methylene chloride (4 x 5 mL). The methylene chloride solution was dried with anhydrous sodium sulfate, concentrated, and the crude product was chromatographed on silica gel to give the product as a yellow liquid. A small amount of ethanol was added and the pure amine **22** was obtained as a white solid (74%) after filtration: mp 114-117 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.66

(d, $J = 4.4$ Hz, 1 H), 7.94 (d, $J = 8.1$ Hz, 2 H), 7.70 (m, 2 H), 7.39 (d, $J = 8.0$ Hz), 7.19 (m, 1 H), 3.90 (s, 2 H), 1.98 (s, 2 H).

Example 18 - Preparation of Compound 23

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A mixture of 2,6-dichloropurine (1.019 g, 1 mmol), amine **22** (0.39 g, 2.15 mmol) in ethanol (13 mL), and water (3.4 mL) was heated at 100-110 °C under nitrogen for 24 h and then it was cooled to room temperature. The mixture was concentrated and water (5 mL) was added. A solid was filtered and washed with
10 water (2 x 5 mL) and dried under vacuum to give the product (93%) as yellow solid: mp 260 °C (dec); ^1H NMR (500 Hz, DMSO- d_6) δ 12.4 (bs, 1 H), 8.76 (m, $J = 1$ Hz, 1 H), 8.28 (s, 1 H), 8.16 (d, $J = 8.1$ Hz, 2 H), 8.03 (d, $J = 7.8$ Hz, 1 H), 7.97 (m, 1 H), 7.58 (d, $J = 8.6$ Hz, 2 H), 7.45 (m, 1 H), 4.82 (s, 2 H).

Example 19 - Preparation of Compound 24

To the solution of compound **23** (0.33 g, 1 mmol) in DMSO (5.2 mL), added potassium carbonate (0.7 g, 5 mmol) and 2-iodopropane (0.5 g, 3 mmol). The mixture was stirred at ambient temperature under nitrogen for 24 h and poured into
20 ice water (30 mL). After filtration, the solid was washed with water (4 x 5 mL), dried under vacuum to give the crude product as a yellow solid. Flash column chromatography of the crude product on silica gel and recrystallization provided the pure product (76%) as white crystals: mp 178-179 °C; ^1H NMR (500 Hz, CDCl_3) δ 8.68 (m, 1 H), 7.96 (d, $J = 8$ Hz, 2 H), 7.76-7.70 (m, 2 H), 7.73 (s, 1 H), 7.47 (d, $J = 8$
25 Hz, 2 H), 7.22 (m, 1 H), 4.89 (s, 1 H), 4.79 (m, 1 H), 1.54 (d, $J = 6.8$ Hz, 6 H); CI MS $m/z = 379$ [$\text{C}_{20}\text{H}_{19}\text{ClN}_6 + \text{H}$] $^+$. Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{ClN}_6$: C, 63.41; H, 5.05; N, 22.18. Found: C, 63.07; H, 5.01; N, 22.01.

Example 20 - Preparation of Compound 17

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To compound **24** (0.7 g, 1.8 mmol) was added (*R*)-(-)-2-amino-1-butanol (3.5 g, 3.9 mmol) stirred in a sealed tube for 2 h at 190 °C. The reaction mixture was allowed to cool and then was partitioned between EtOAc and brine. The EtOAc was separated, washed with saturated brine (4 x), dried with Na_2SO_4 , and

concentrated. The product was air dried to give an oil, then dissolved in EtOAc. The EtOAc solution was cooled again, and the precipitate collected, washed with cold EtOAc (2 x), air dried, and heated *in vacuo* for 2 h to give **17** (0.54 g, 67%): mp 98-100 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.85 (m, 2 H), 7.75-7.55 (m, 2 H), 7.50-7.35 (m, 3 H), 7.30-7.15 (m, 1 H), 6.40-6.20 (bs, 1 H), 5.00-4.82 (m, 1 H), 4.80-4.68 (bs, 3 H), 4.60 (heptuplet, 1 H), 3.98-3.70 (m, 2 H), 3.70-3.54 (dd, 1 H), 2.10 (bs, 1 H), 1.75-1.53 (m, 2 H), 1.51 (d, 6 H), 1.00 (t, 3 H); IR (KBr) 3406, 2969, 1601, 1490, 1389, 1254, 779 cm⁻¹; API MS *m/z* = 432 [C₂₄H₂₉N₇O+H]⁺.

10 **Example 21 - Preparation of Compound 25**

To compound **4** (0.14 g, 0.33 mmol) was added 3-(tributylstannyl)pyridine (0.15 g, 0.33 mmol), Pd(PPh₃)₄ (0.06 g, 0.41 mmol), and toluene (10 mL). The solution was degassed with argon for 8 min in a sealed tube, and heated in an oil bath for 3 h at 130 °C. The cooled reaction mixture was diluted with saturated NaHCO₃ and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄. The reaction mixture was purified by column chromatography on silica gel to give the desired coupling product. The product was dissolved in acetonitrile and washed with hexane (3 x 10 mL) to remove a portion of the tin contaminants. The reaction mixture was again purified by column chromatography on reversed phase silica gel to give compound **25** (0.04 g): ¹H NMR (300 MHz, CDCl₃) δ 8.83 (s, 1 H), 8.58 (d, 1 H), 7.88-7.83 (m, 1 H), 7.56-7.46 (m, 5 H), 7.38-7.33 (m, 1 H), 5.99 (s, 1 H), 5.11 (s, 1 H), 4.90-4.83 (m, 2 H), 4.63-4.56 (m, 1 H), 3.92-3.81 (m, 2 H), 3.67-3.60 (m, 1 H), 1.69-1.49 (m, 8 H), 1.05-1.00 (t, 3 H); CI MS *m/z* = 432 [C₂₄H₂₉N₇O+H]⁺.

Example 22 - Preparation of Compound 27

A mixture of diethyl(3-pyridyl)borane (**26**, 540 mg, 3.67 mmol), 4-bromobenzonitrile (803 mg, 4.41 mmol) and Pd(PPh₃)₄ (144 mg, 0.13 mmol) in toluene (9 mL), ethanol (1.3 mL) and 2M aqueous sodium carbonate solution (4.1 mL, 8.2 mmol) was heated at 90-100 °C under nitrogen for 27 h. The mixture was cooled to room temperature and water (10 mL) was added. The organic layer was

separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL) and dried over anhydrous sodium sulfate. Flash chromatography of the crude product on silica gave the product as a white solid (80%): mp 95-96 °C.

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Example 23 - An Alternative Preparation of 27 is Described Below

A flask charged with 4-bromobenzonitrile (360 mg, 2.0 mmol), bis(pinacolato)diboron (560 mg, 2.2 mmol), potassium acetate (590 mg, 6.0 mmol) and PdCl₂(dppf) (49 mg, 0.06 mmol) was flushed with nitrogen and DMF (12 mL) was added. The mixture was heated at 80-85 °C for 4 h and then cooled to room temperature at which time PdCl₂(dppf) (49 mg, 0.06 mmol), 3-bromopyridine (385 δL, 3.40 mmol), and 2M aqueous sodium carbonate solution (5 mL, 10 mmol) was added. The mixture was stirred at 80-85 °C for 24 h and extracted with ethyl ether (3 x 30 mL) and then washed with brine (3 x 15 mL) and dried with anhydrous sodium sulfate. Flash chromatography of the crude product on silica gel gave the product as white crystals (56%): mp 96-97 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.55 (dd, J₁ = 1 Hz, J₂ = 1.4 Hz, 1 H), 8.66 (m, 1 H), 7.90-7.87 (m, 1 H), 7.77 (d, J = 7.8 Hz, 2 H), 7.69 (d, J = 8.8 Hz, 2 H), 7.42 (m, 1 H).

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Example 24 - Preparation of Compound 28

To LiAlH₄ (8 mmol) in THF (25 mL) was added 27 (0.96 g, 5.3 mmol) in THF (25 mL) slowly while the flask was cooled with ice. The mixture was stirred at room temperature for 10-30 min then stirred at reflux for 4 h under nitrogen. The mixture was cooled in an ice bath and aqueous sodium hydroxide solution (0.5 mL, 10%) was added. The mixture was stirred until the residue became white and the solid was filtered and washed with methylene chloride (4 x 5 mL). The methylene chloride solution was dried with anhydrous sodium sulfate, concentrated, and the crude product was chromatographed on silica gel to give the product as a yellow liquid. A small amount of ethanol was added and the pure amine 28 was obtained as a white solid (46%) after filtration: mp 94-96 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.74 (d,

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$J = 2.4$ Hz, 1 H), 8.48 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.7$ Hz, 1 H), 7.77 (m, 1 H), 7.45 (d, $J = 8.10$ Hz, 2 H), 7.33 (d, $J = 8.0$ Hz, 2 H), 7.25 (m, 1 H), 3.83 (s, 2 H), 2.25 (s, 2 H).

Example 25 - Preparation of Compound 29

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A mixture of 2,6-dichloropurine (**1**, 0.19 g, 1 mmol), amine **28** (0.4 g, 2.15 mmol) in ethanol (13 mL), water (3 mL) was heated at 100-110 °C under nitrogen for 24 h and then it was cooled to room temperature. The mixture was concentrated and water (5 mL) was added. A solid was filtered and washed with
10 water (2 x 5 mL) and dried under vacuum to give the product (92%) as a yellow solid: mp 219 °C (dec); ^1H NMR (500 Hz, DMSO- d_6) δ 13.2 (bs, 1 H), 8.99 (s, 1 H), 8.66 (d, $J = 3.5$ Hz, 1 H), 8.28 (s, 1 H), 8.16 (d, $J = 7.3$ Hz, 1 H), 7.80 (d, $J = 7.6$ Hz, 2 H), 7.60-7.57 (m, 3 H).

Example 26 - Preparation of Compound 30

To a solution of **29** (0.3 g, 1 mmol) in DMSO (5 mL), was added potassium carbonate (0.7 g, 5 mmol) and 2-iodopropane (0.5 g, 3 mmol). The mixture was stirred at ambient temperature under nitrogen for 24 h and poured into
20 ice water (30 mL). After filtration, the solid was washed with water (4 x 5 mL), dried under vacuum to give the crude product as a yellow solid. Flash column chromatography of the crude product on silica gel and recrystallization provided the pure product (76%) as white crystals: mp 178-179 °C; ^1H NMR (500 Hz, CDCl_3) δ 8.82 (d, $J = 1.3$ Hz, 1 H), 8.59-8.58 (m, 1 H), 7.86-7.84 (m, 1 H), 7.72 (s, 1 H), 7.56-
25 7.48 (m, 4 H), 7.37-7.34 (m, 1 H), 4.88 (s, 2 H), 4.82 (m, 1 H), 1.56 (d, $J = 0.7$ Hz, 3 H), 1.55 (d, $J = 0.8$ Hz, 3 H); CI MS $m/z = 379$ [$\text{C}_{20}\text{H}_{19}\text{ClN}_6 + \text{H}$] $^+$. Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{ClN}_6$: C, 63.41; H, 5.05; N, 22.18. Found: C, 63.24; H, 4.97; N, 21.93.

Example 27 - Preparation of Compound 32

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To a mixture of **4** (0.05 g, 0.11 mmol) was added 4-(tributylstannyl)pyridine (0.06 g, 0.16 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.02 g, 0.02 mmol), and toluene (2.5 mL). The reaction mixture was degassed and heated in a sealed tube at 125 °C for 3 h. The reaction mixture was cooled to room temperature then saturated

NaHCO₃ (30 mL) was added followed by extraction with CH₂Cl₂ (3 x 30). The organic layer was washed with brine (50 mL), dried with MgSO₄, and concentrated. The reaction mixture was purified by column chromatography on silica gel to give **32**:
¹H NMR (300 MHz, CDCl₃) δ 8.65 (s, 2 H), 7.60-7.57 (m, 2 H), 7.49-7.45 (m, 5 H),
5 6.20 (s, 1 H), 4.93 (d, 1 H), 4.84 (s, 2 H), 4.65-4.57 (m, 1 H), 3.92-3.80 (m, 2 H),
3.68-3.51 (m, 1 H), 1.68-1.58 (m, 2 H), 1.52 (d, 6 H), 1.05-0.99 (t, 3 H).

Example 28 - Preparation of Compound 33

10 To compound **4** (0.18 g, 0.43 mmol) was added 4-vinylphenylboronic acid (0.19 g, 1.28 mmol), Pd(PPh₃)₄ (0.09 g, 0.08 mmol), Na₂CO₃ (2M, 0.85 mL), was added toluene (5 mL). The mixture was degassed with argon for 10 min. The resulting solution was heated in a sealed tube at 135 °C for 4.5 h. The cooled solution was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The combined
15 organic extracts were washed with brine and dried over Na₂SO₄. The solution was purified by flash column chromatography (2 x) on silica gel to give the desired product **33** as a yellow solid (0.09 g): mp 130-131 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.57-7.42 (m, 9 H), 6.80-6.70 (dd, 1 H), 5.98 (s, 1 H), 5.79 (d, 1 H), 5.27 (d, 1 H), 4.88 (d, 1 H), 4.84-4.72 (m, 2 H), 4.63-4.56 (m, 1 H), 3.92-3.81 (m, 2 H), 3.66-3.60
20 (m, 1 H), 1.68-1.52 (m, 8 H), 1.05-1.00 (t, 3 H); IR (CH₂Cl₂) 3293, 2968, 1601, 1489, 1390 cm⁻¹; CI MS *m/z* = 457 [C₂₇H₃₂N₆O+H]⁺.

Example 29 - Preparation of Compound 34

25 To compound **33** (0.008 g, 0.016 mmol) was added OsO₄ (0.007 g, 0.026 mmol), pyridine (0.08 mL), and toluene (0.75 mL). The reaction mixture was stirred at room temperature in the dark for 1 h, concentrated *in vacuo*, and then slurried in methanol/water (9:1). Sodium metabisulfite (0.07 g) was added and the reaction was stirred for 1 h. The mixture was washed with brine, extracted with
30 CH₂Cl₂ (3 x 10 mL), dried over Na₂SO₄, and concentrated. The product was purified by column chromatography on silica gel to give compound **34** (0.003 g) as a tan solid: ¹H NMR (300 MHz, CDCl₃) δ 7.51 (s, 1 H), 7.43-7.35 (m, 6 H), 7.25-7.22 (m, 2 H).

6.51 (s, 1 H), 4.98 (d, 1 H), 4.35-4.25 (m, 2 H), 4.64-4.54 (m, 1 H), 3.93-3.80 (m, 3 H), 3.74-3.59 (m, 3 H), 1.68-1.58 (m, 2 H), 1.52 (d, 6 H), 1.06-0.99 (t, 3 H).

Example 30 - Preparation of Compound 36

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To compound **4** (0.12 g, 0.27 mmol) was added 3-aminophenylboronic acid hydrochloride (0.12 g, 0.69 mmol), and Pd(PPh₃)₄ (0.09 g, 0.75 mmol) in a sealed tube filled with argon. To this mixture was added toluene (5 mL) and Na₂CO₃ (2M, 0.55 mL). The resulting solution was degassed with argon for 5 min and placed
10 in a 130 °C oil bath for 6 h. The cooled solution was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The solution was purified by column chromatography on silica gel to yield **36** (0.04 g, 36%): ¹H NMR (300 MHz, CDCl₃) δ 7.52-7.46 (m, 3 H), 7.39 (d, 2 H), 7.23-7.18 (m, 1 H), 6.96 (d, 1 H), 6.88 (t, 1 H),
15 6.68-6.66 (m, 1 H), 6.12 (s, 1 H), 4.90 (d, 1 H), 4.79 (s, 2 H), 4.62-4.57 (m, 1 H), 3.92-3.76 (m, 4 H), 3.66-3.60 (m, 1 H), 1.65-1.48 (m, 8 H), 1.04-0.99 (t, 3 H); CI MS *m/z* = 446 [C₂₅H₃₁N₇O+H]⁺.

Example 31 - Preparation of Compound 38

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To a suspension of Pd(PPh₃)₄ (0.02 g, 0.01 mmol) in anhydrous DME (8 mL) was added **4** (0.12 g, 0.27 mmol) and the mixture stirred at room temperature for 10 min. To this solution was added 3-(trifluoromethyl)phenylboronic acid (**37**; 0.12 g, 0.65 mmol) in a minimum of EtOH, followed by Na₂CO₃ (2M, 0.27 mL), and
25 the resulting mixture was heated at reflux for 20 h. The cooled reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The reaction mixture was purified by column chromatography on normal phase silica gel followed by reversed phase column chromatography to obtain **38** (0.04 g, 33%) as an off white
30 solid: mp 60-67 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (s, 1 H), 7.74 (d, 1 H), 7.58-7.45 (m, 7 H), 5.98 (s, 1 H), 4.90-4.83 (m, 3 H), 4.63-4.59 (m, 1 H), 3.90-3.81 (m, 2 H), 3.66-3.60 (m, 1 H), 1.68-1.51 (m, 8 H), 1.05-1.00 (t, 3 H); IR (KBr) 3406, 2969, 1602, 1489, 1335 cm⁻¹; CI MS *m/z* = 499 [C₂₆H₂₉FN₇O+H]⁺.

Example 32 - Preparation of Compound 40

A mixture of **4** (0.13 g, 0.31 mmol), 2-naphthaleneboronic acid (**39**; 0.11 g, 0.62 mmol) and Pd(PPh₃)₄ (0.09 g, 0.08 mmol) was placed in a sealed tube that was filled with argon. To the mixture was added toluene (5 mL) and Na₂CO₃ (2M, 0.62 mL). The tube was quickly sealed and heated at 125 °C in an oil bath for 6 h. The cooled solution was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The reaction mixture was purified by column chromatography on normal phase silica gel, followed by reversed phase chromatography to give **40** (0.04 g, 28%): mp 70-75 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 1 H), 7.92-7.84 (m, 3 H), 7.74-7.67 (m, 3 H), 7.51-7.44 (m, 5 H), 5.96 (s, 1 H), 4.89-4.84 (m, 3 H), 4.66-4.57 (m, 1 H), 3.93-3.82 (m, 2 H), 3.67-3.61 (m, 1 H), 1.76-1.50 (m, 8 H), 1.06-1.01 (t, 3 H); IR (KBr) 3422, 2927, 1601, 1491, 1388 cm⁻¹.

Example 33 - Preparation of Compound 43

To compound **4** (0.14 g, 0.33 mmol) was added 4-methoxyphenylboronic acid (**42**, 0.11 g, 0.71 mmol), Pd(PPh₃)₄ (0.10 g, 0.087 mmol), Na₂CO₃ (2M, 0.66 mL), and toluene (7 mL). The solution was degassed for 8 min with argon and heated in an oil bath at 125 °C for 6 h. The cooled solution was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The reaction mixture was purified by normal phase column chromatography followed by reversed phase chromatography to give **43** (0.05 g, 28%) as a white solid: mp 128-130 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.52-7.50 (m, 5 H), 7.41 (d, 2 H), 6.97 (d, 2 H), 5.93 (s, 1 H), 4.89-4.79 (m, 3 H), 4.63-4.56 (m, 1 H), 3.92-3.81 (m, 5 H), 3.67-3.60 (m, 1 H), 1.68-1.49 (m, 8 H), 1.05-1.00 (t, 3 H); IR (KBr) 3417, 2931, 1610, 1499, 1389 cm⁻¹; CI MS *m/z* = 461 [C₂₆H₃₂N₆O₂+H]⁺.

Example 34 - Preparation of Compound 45

To a solution of *s*-BuLi (5 mL, 6.24 mmol) and TMEDA (1 mL) in anhydrous THF (35 mL) at -75 °C under argon was added dropwise a solution of *N,N*-diethylbenzamide (0.98 g, 5.57 mmol) in THF (5 mL). The mixture was stirred for 50 min and then treated with trimethylborate (2 mL, 17 mmol). The solution was allowed to warm to room temperature overnight. The colorless solution was cooled to 0 °C and acidified to pH = 6 with 2N HCl. The THF was removed *in vacuo* and the residue was diluted with water. This was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, concentrated *in vacuo*, followed by removal of trace solvent on the vacuum pump to give **45** as an off-white foamy solid: ¹H NMR (300 MHz, CD₃OD) δ 7.67-7.39 (m, 4 H), 3.88-3.69 (q, 4 H), 1.41-1.30 (t, 6 H).

Example 35 - Preparation of Compound 46

To compound **4** (0.14 g, 0.31 mmol) was added 2-(diethylcarbamoyl)phenylboronic acid (**45**, 0.29 g, 1.31 mmol), Pd(PPh₃)₄ (0.1 g, 0.09 mmol), Na₂CO₃ (2M, 0.63 mL), toluene (5 mL), and the mixture degassed with argon for 10 min. The mixture was heated in an oil bath for 5 h at 135 °C. The cooled solution was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na₂CO₃, and concentrated. The reaction mixture was purified by normal phase column chromatography on silica gel, followed by reversed phase chromatography to give **46** (0.03 g, 18%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 7.49-7.36 (m, 9 H), 6.18 (s, 1 H), 4.93 (d, 1 H), 4.78 (s, 2 H), 4.64-4.55 (m, 1 H), 3.92-3.60 (m, 4 H), 3.06-2.92 (m, 2 H), 2.69-2.64 (m, 1 H), 1.68-1.51 (m, 8 H), 1.04-0.99 (t, 3 H), 0.91-0.86 (t, 3 H), 0.77-0.72 (t, 3 H); CI MS *m/z* = 530 [C₃₀H₃₉N₇O₂+H]⁺.

Example 36 - Preparation of Compound 48

To a suspension of Pd(PPh₃)₄ (0.08 g, 0.69 mmol) in DME was added **4** (0.129 g, 0.30 mmol) and the mixture stirred for 10 min at room temperature. To this was added 3-nitrophenylboronic acid (**47**, 0.157 g, 0.94 mmol) and Na₂CO₃ (2 M,

0.59 mL). The solution was heated at reflux under argon overnight. The cooled solution was diluted with water and extracted with CH₂Cl₂ (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The solution was purified by flash column chromatography on silica gel to give **48** (0.04 g, 29%) as a bright yellow solid: mp 73-77 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.43 (s, 1 H), 8.20 (d, 1 H), 7.89 (d, 1 H), 7.63-7.43 (m, 6 H), 6.01 (s, 1 H), 4.95-4.76 (m, 3 H), 4.68-4.58 (m, 1 H), 3.98-3.80 (m, 2 H), 3.68-3.60 (m, 1 H), 1.71-1.40 (m, 8 H), 1.02-0.98 (t, 3 H); IR (KBr) 3405, 2930, 1713, 1602, 1490, 1351 cm⁻¹; CI MS *m/z* = 476 [C₂₅H₂₉N₇O₃+H]⁺.

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Example 37 - Preparation of Compound 50

To a suspension of Pd(PPh₃)₄ (0.09 g, 0.08 mmol) in DME (5 mL) was added **4** (0.14 g, 0.32 mmol) and the mixture stirred at room temperature for 15 min. To this was added benzo[b]furan-2-boronic acid (**49**, 0.153 g, 0.94 mmol) and Na₂CO₃ (2 M, 0.63 mL). The solution was heated at reflux under argon overnight. The reaction mixture was cooled, diluted with water, extracted with CH₂Cl₂ (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The solution was purified by flash column chromatography on silica gel followed by flash column chromatography on reversed phase silica to give **50** (0.09 g, 60%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, 2 H), 7.58-7.42 (m, 5 H), 7.30-7.19 (m, 2 H), 7.01 (s, 1 H), 6.11 (s, 1 H), 4.91 (d, 1 H), 4.81 (s, 2 H), 4.62-4.58 (m, 1 H), 3.92-3.80 (m, 2 H), 3.66-3.60 (m, 1 H), 1.66-1.48 (m, 8 H), 1.04-0.99 (t, 3 H); CI MS *m/z* = 471 [C₂₇H₃₀N₆O₂+H]⁺.

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Example 38 - Preparation of Compound 52

To compound **4** (0.46 g, 1.20 mmol) was added 1-amino-1-cyclopentanemethanol (**51**, 1.0 g, 8.61 mmol) and EtOH (2 mL) and the mixture was heated in an oil bath at 150 °C for 60 h. The brown solution was cooled and heated again at 150 °C for 48 h. The reaction mixture was cooled and concentrated *in vacuo*. The reaction mixture was purified by flash column chromatography on silica gel to give **52** (0.39 g, 71%) as a tan solid: ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.40 (m, 3

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H), 7.29-7.20 (m, 2 H), 6.88 (s, 1 H), 6.25 (s, 1 H), 5.10 (s, 1 H), 4.72 (s, 2 H), 4.63-4.51 (m, 1 H), 3.78 (s, 2 H), 2.10-1.65 (m, 8 H), 1.54 (d, 6 H); CI MS m/z = 459 $[C_{21}H_{27}BrN_6O+H]^+$.

5 **Example 39 - Preparation of Compound 53**

To a suspension of $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) in DME (5 mL) was added **52** (0.102 g, 0.22 mmol) and stirred at room temperature for 15 min. To this was added phenylboronic acid (0.098 g, 0.80 mmol) and Na_2CO_3 (2 M, 0.44 mL).
10 The solution was heated at reflux under argon for 18 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2 (3 x 50 mL), washed with brine, and dried over Na_2SO_4 . The solution was purified by flash column chromatography on silica gel followed by flash column chromatography on reversed phase silica gel to give **53** (0.02 g, 20%): 1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.31 (m, 10 H), 6.95 (s, 1 H), 5.95
15 (s, 1 H), 5.10 (s, 1 H), 4.79 (s, 2 H), 4.61-4.52 (m, 1 H), 3.76 (s, 2 H), 2.01-1.61 (m, 8 H), 1.54 (d, 6 H); CI MS m/z = 457 $[C_{27}H_{32}N_6O+H]^+$.

Example 40 - Preparation of Compound 54

20 To compound **3** (0.26 g, 0.67 mmol) was added *trans*-4-aminocyclohexanol hydrochloride (0.62 g, 4.11 mmol), Et_3N (0.58 mL, 4.16 mmol), and ethanol (5 mL). The mixture was heated for 5 h at 135 °C in an oil bath. The temperature increased to 150 °C and heating was continued for a further 48 h. The solution was cooled and evaporated to give a yellow oil: CI MS m/z = 459
25 $[C_{21}H_{27}BrN_6O+H]^+$.

Example 41 - Preparation of Compound 55

To compound **3** (0.50 g, 1.31 mmol) was added *cis*-1,2-diaminocyclohexane (1.57 mL, 13.1 mmol) and EtOH (4 mL). The mixture was
30 heated in an oil bath at 150 °C for 6 h. The reaction mixture was concentrated *in vacuo*. The reaction mixture was purified by column chromatography on silica gel to give **55** (0.49 g, 82%) as a yellow solid: 1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.40 (m, 3 H), 7.23 (d, 2 H), 6.21 (s, 1 H), 5.04 (d, 1 H), 4.72 (s, 2 H), 4.67-4.58 (m, 1 H).

4.08-4.05 (m, 1 H), 3.17-3.15 (m, 1 H), 2.08 (s, 2 H), 1.65-1.38 (m, 14 H); CI MS m/z = 458 $[C_{21}H_{28}BrN_7+H]^+$.

Example 42 - Preparation of Compound 56

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To compound **55** (0.10 g, 0.22 mmol) was added 2-(tributylstannyl)pyridine (0.10 g, 0.27 mmol), $Pd(PPh_3)_4$ (0.05 g, 0.04 mmol), and toluene (5 mL). The solution was degassed with argon for 8 min and heated at 135 °C for 3 h. The cooled solution was diluted with water, extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The solution was followed by flash column chromatography (2 x) to give the desired product **56** (0.03 g, 36%) yellow crystalline solid: 1H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, 1 H), 7.96 (d, 2 H), 7.78-7.69 (m, 2 H), 7.49 (s, 1 H), 7.44 (d, 2 H), 7.23-7.18 (m, 1 H), 6.10 (s, 1 H), 5.10-5.00 (m, 1 H), 4.83 (s, 2 H), 4.69-4.60 (m, 1 H), 4.20-4.10 (m, 1 H), 3.27-3.13 (m, 1 H), 2.48 (s, 2 H), 1.78-1.42 (m, 14 H); CI MS m/z = 457 $[C_{26}H_{32}N_8+H]^+$.

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Example 43 - Preparation of Compound 57

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To compound **1** (0.50 g, 1.31 mmol) was added *trans*-1,2-diaminocyclohexane (2.52 mL, 21 mmol), and EtOH (6 mL). The reaction mixture was placed in an oil bath and heated to 190 °C for 25 h. The reaction mixture was removed from the heat and cooled to room temperature, concentrated for purification. The reaction mixture was purified by column chromatography on silica gel to yield **57** (520 mg, 87%) as an off white foam: 1H NMR (300 MHz, DMSO) δ 7.95 (bs, 1 H), 7.85 (s, 1 H), 7.50 (d, 2 H), 7.34 (d, 2 H), 6.17 (d, 1 H), 4.70-4.40 (m, 1 H), 2.00-1.71 (m, 4 H), 1.70-1.52 (m, 2 H), 1.41 (d, 6 H), 1.30-0.92 (m, 4 H); API MS m/z = 460 $[C_{21}H_{28}N_7Br+H]^+$.

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Example 44 - Preparation of Compound 58

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Compound **57** (0.15 g, 0.32 mmol) was added to a suspension of $Pd(PPh_3)_4$ (0.11 g, 0.1 mmol) in DME (7 mL) and stirred at room temperature for 15 min. Phenylboronic acid (0.14 g, 1.14 mmol) was added followed by the Na_2CO_3

(2M, 0.62 mmol). The reaction mixture was refluxed under argon for 18 h and allowed to stir at room temperature for 51 h. It was then diluted with water, extracted with CH₂Cl₂, washed with brine, and then extracted with CH₂Cl₂. The organic layer was evaporated, dried over anhydrous Na₂SO₄, purified by column chromatography, and placed *in vacuo* for 18 h to give **58** (0.10 g, 72%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.35 (m, 10 H), 5.92 (br, 1 H), 4.83 (br, 2 H), 4.74-4.56 (m, 2 H), 3.77-3.55 (m, 1 H), 2.55-2.43 (m, 1 H), 2.16-1.91 (m, 2 H), 1.73 (br, 2 H), 1.52 (d, 6 H), 1.37-1.09 (m, 6 H); API MS *m/z* = 456 [C₂₇H₃₃N₇+H]⁺.

10 **Example 45 - Preparation of Compound 59**

To compound **57** (460 mg, 1.0 mmol) in solution with CH₂Cl₂ (2 mL) was added acetic anhydride (0.44 mL, 4.6 mmol), catalytic DMAP, and pyridine (0.5 mL). The mixture was stirred at room temperature for 2.5 h. The mixture was diluted with CH₂Cl₂, washed with 2N HCl, and the combined organics were then washed with NaHCO₃. The organics were then washed with brine, dried over Na₂SO₄, filtered, and concentrated to give **59** (472 mg, 94%) as an off white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.76 (s, 1 H), 7.42 (d, 2 H), 7.29 (d, 2 H), 4.68-4.40 (m, 1 H), 4.10 (s, 3 H), 3.61-3.40 (m, 2 H), 2.15-1.80 (m, 2 H), 1.74-1.55 (m, 4 H), 1.45 (d, 6 H), 1.35-1.05 (m, 4 H); API MS *m/z* = 500 [C₂₃H₃₀BrN₇O+H]⁺.

Example 46 - Preparation of Compound 60

To a suspension of Pd(PPh₃)₄ (0.11 g, 0.1 mmol) in DME (7 mL) was added compound **59** (0.15 g, 0.3 mmol) and stirred at room temperature for 15 min under argon. Phenylboronic acid (0.13 g, 1.06 mmol) was added, followed by Na₂CO₃ (2M, 0.62 mL). The reaction mixture was refluxed under argon for 18 h. The reaction mixture was then diluted with H₂O, extracted with CH₂Cl₂, washed with brine, and extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄, purified by column chromatography, concentrated *in vacuo* for 18 h to yield **60** (61 mg, 42%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.96 (s, 1 H), 7.72 (s, 1 H), 7.51 (t, 3 H), 7.40-7.28 (m, 3 H), 7.28-7.13 (m, 2 H), 5.84 (br, 1 H), 4.46 (br, 3 H), 3.47

(br. 2 H), 1.83 (br. 1 H), 1.62 (s. 4 H), 1.43 (d. 6 H), 0.12 (s. 3 H); API MS m/z = 498 $[C_{29}H_{35}N_7O+H]^+$.

Example 47 - Preparation of Compound 61

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To compound **3** (0.58 g, 1.53 mmol) was added *trans*-1,4-diaminocyclohexane (1.78 g, 15.6 mmol), and EtOH (4 mL). The mixture was heated in an oil bath at 150 °C for ca. 60 h. The reaction mixture was purified by column chromatography on silica gel to yield **61** (0.48 g, 68%) as an off white solid: mp 122-125 °C; 1H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1 H), 7.40 (d, 2 H), 7.20 (d, 2 H), 6.27 (s, 1 H), 4.75-4.68 (m, 2 H), 4.67-4.58 (m, 2 H), 3.81-3.68 (m, 1 H), 3.45 (s, 2 H), 2.88-2.75 (m, 1 H), 2.18-2.05 (m, 2 H), 2.05-1.89 (m, 2 H), 4.52 (d, 6 H), 1.45-1.13 (m, 4 H); CI MS m/z = 459 $[C_{21}H_{28}BrN_7+H]^+$.

Example 48 - Preparation of Compound 62

Amine **61** (53 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2 mL) and pyridine (5 mL). Acetic anhydride (0.05 g, 0.53 mmol) and DMAP (few crystals) were added. The reaction mixture was allowed to stir at room temperature for 2.25 h. The reaction mixture was diluted with CH_2Cl_2 , washed with 2N HCl, $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to yield **62** (0.05 g, 78%) as a white solid: 1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.20 (m, 5 H), 6.02 (br. 1 H), 5.29-5.20 (m, 1 H), 4.72 (d, 2 H), 4.66-4.54 (m, 2 H), 3.72 (br, 2 H), 2.18-2.06 (m, 2 H), 2.06-1.91 (m, 2 H), 1.97 (s, 3 H), 1.54 (d, 6 H), 1.36-1.15 (m, 4 H); API MS m/z = 500 $[C_{23}H_{30}BrN_7O+H]^+$.

Example 49 - Preparation of Compound 64

Compound **61** (0.05 g, 0.11 mmol) was dissolved in CH_2Cl_2 (3 mL) and Et_3N (2 mL) and placed in an ice bath for 10 min. Compound **63** (0.06 g, 0.22 mmol) was dissolved in CH_2Cl_2 (2 mL), added dropwise, and rinsed with CH_2Cl_2 (1.5 mL). The ice bath was removed after 20 min and the reaction was allowed to stir for 7 d. The reaction mixture was diluted with CH_2Cl_2 , washed with 2N HCl until the aqueous layer was acidic, washed with $NaHCO_3$, dried over $MgSO_4$, and evaporated.

The desired product was isolated by column chromatography and dried *in vacuo* to yield **64** (0.04 g, 50%) as a green solid: ^1H NMR (300 MHz, CDCl_3) δ 8.53 (d, 1 H), 8.32-8.20 (m, 2 H), 7.59-7.35 (m, 4 H), 7.23-7.11 (m, 4 H), 6.02 (br, 1 H), 4.69-4.45 (m, 5 H), 3.57 (br, 1 H), 3.12 (br, 1 H), 2.87 (s, 1 H), 1.97 (br, 2 H), 1.75 (br, 2 H), 1.48 (d, 6 H), 1.27-0.97 (m, 4 H); API MS m/z = 693 $[\text{C}_{33}\text{H}_{39}\text{BrN}_8\text{O}_2\text{S}+\text{H}]^-$.

Example 50 - Preparation of Compound 65

Compound **61** (0.05 g, 0.11 mmol) was dissolved in CH_2Cl_2 (3 mL) and Et_3N (2 mL) and placed in an MeOH/ice bath. Methanesulfonyl chloride (0.012 mg, 0.11 mmol) in CH_2Cl_2 (2.3 mL) was slowly added. The reaction mixture and ice bath was allowed to come to room temperature. After 1.5 h, the reaction mixture was diluted with CH_2Cl_2 , washed with 2N HCl until the aqueous layer was acidic. The organic layer was washed with NaHCO_3 , dried over MgSO_4 , filtered, and evaporated. The product was purified by column chromatography, and dried *in vacuo* for 14 h to yield **65** (13 mg, 24%) as an off-white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.50-7.17 (m, 5 H), 5.90 (br, 1 H), 4.75-4.57 (m, 3 H), 4.11 (d, 1 H), 3.69 (br, 1 H), 3.30 (br, 1 H), 2.99 (s, 3 H), 2.18-2.03 (m, 4 H), 1.69 (d, 6 H), 1.42-1.15 (m, 5 H); API MS m/z = 538 $[\text{C}_{22}\text{H}_{30}\text{BrN}_7\text{O}_2\text{S}+\text{H}]^+$.

Example 51 - Preparation of Compound 66

Compound **61** (0.05 g, 0.11 mmol) was dissolved in toluene (4 mL). 2-Acetylphenylisocyanate (0.024 g, 0.15 mmol) diluted with toluene (1 mL) and added to compound **61**. Toluene (6 mL) was added to the reaction mixture. The reaction mixture was placed under reflux for 19 h. The product was purified by column chromatography, concentrated, and dried *in vacuo* for 23 h to yield **66** (42 mg, 62%) as an off-white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.87-7.20 (m, 9 H), 6.41 (s, 1 H), 5.86 (br, 1 H), 4.75-4.54 (m, 4 H), 3.69 (br, 1 H), 2.60 (s, 3 H), 2.12 (br, 4 H), 1.51 (d, 6 H), 1.42-1.15 (m, 5 H); API MS m/z = 619 $[\text{C}_{30}\text{H}_{35}\text{BrN}_8\text{O}_2+\text{H}]^+$.

Example 52 - Preparation of Compound 67

Compound **61** (0.04 g, 0.10 mmol) was dissolved in CH₂Cl₂ (2 mL) and pyridine (0.5 mL). Cyclopropanecarbonyl chloride (0.05 g, 0.44 mmol) was added along with DMAP (small amount). The reaction mixture was allowed to stir at room temperature for 2.25 h. The reaction mixture was diluted with CH₂Cl₂, washed with 2N HCl, saturated NaHCO₃, dried over MgSO₄, filtered, and evaporated. The product was isolated by column chromatography to yield **67** (0.03 g, 63%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.50-7.20 (m, 5 H), 5.96 (br, 1 H), 5.41 (d, 1 H), 4.72 (d, 2 H), 4.66-4.54 (m, 2 H), 3.72 (br, 2 H), 2.18-1.97 (m, 4 H), 1.51 (d, 6 H), 1.36-1.15 (m, 5 H), 1.06-0.88 (m, 2 H), 0.79-0.67 (m, 2 H); API MS *m/z* = 526 [C₂₅H₃₂BrN₇O+H]⁺.

Example 53 - Preparation of Compound 69

To a solution of 4-biphenylcarboxaldehyde (1.0 g, 5.49 mmol) in MeOH (20 mL) was added NaBH₃CN (0.69 g, 11.0 mmol), and NH₄OH (15 mL) and the mixture was stirred at room temperature overnight. To this added HCl and extracted with CHCl₃. The resulting aqueous layer was brought to pH > 7 with sodium bicarbonate and then extracted with CHCl₃. The solution was dried with MgSO₄, filtered, and evaporated to give **69** (200 mg) as a white solid: EI MS *m/z* = 183 [C₁₃H₁₃N]⁺.

Example 54 - Preparation of Compound 69

To compound **70** (2.75 g, 13.9 mmol) was added anhydrous THF (60 mL), heated to reflux, and kept under nitrogen. 1M Borane-THF (69.7 mL) was added dropwise to **70** through an addition funnel resulting in a homogeneous solution. The solution was refluxed for 18 h. The reaction mixture was cooled in an ice water bath and quenched with H₂O, 2N HCl (20 mL), followed by 3N NaOH (60 mL). The reaction mixture was extracted with EtOAc (3 x). The organic extracts were washed with brine, and dried over sodium sulfate. The crude product was concentrated, dissolved in MeOH, and HCl gas was bubbled through the solution. The solution was

filtered *in vacuo* to give **69** as a white solid: ^1H NMR (300 MHz, CD_3OD) δ 7.71 (d, 2 H), 7.63 (d, 2 H), 7.52 (d, 2 H), 7.47-7.30 (m, 3 H), 4.13 (s, 2 H).

Example 55 - Preparation of Compound 71

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To compound **1** (6.8 g, 36.0 mmol) and **69** (8.0 g, 36.5 mmol) was added H_2O (60 mL) and Hünigs base (9.0 g, 70.0 mmol). The mixture was stirred and heated to reflux for 5 h during which time H_2O (50 mL) was added as the reaction continued to thicken. The crude product was collected by filtration, washed with H_2O (500 mL) and EtOH (2 x 30 mL), air dried, and dried *in vacuo* to give **71** (11.1 g, 92%); mp 267-269 °C.

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Example 56 - Preparation of Compound 72

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Compound **71** (4.7 g, 14.0 mmol), K_2CO_3 (15.0 g, 109 mmol), DMSO (80 mL), and 2-iodopropane (9.4 g, 55.0 mmol) were combined and stirred overnight. H_2O and EtOAc were added. The EtOAc layer was separated and washed with brine (3 x). The EtOAc solution was dried with MgSO_4 , concentrated, and crystallized from EtOAc to give **72** (3.5 g, 66%); mp 139-140 °C.

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Example 57 - Preparation of Compound 73

Compound **72** (2.00 g, 5.30 mmol) and (*R*)-(-)-2-amino-1-butanol (10.8 g, 121 mmol) were combined in a sealed tube, and heated in an oil bath at 190 °C for 2 h. The solution was cooled to 60 °C, diluted in EtOAc, washed with brine (4 x), dried with Na_2SO_4 , and concentrated. Purification by column chromatography on SiO_2 gave the desired product **73** (1.72 g, 75%) as a foam: ^1H NMR (300 MHz, CDCl_3) δ 7.65-7.10 (m, 9 H), 6.40-6.10 (bs, 1 H), 5.05-4.85 (m, 1 H), 4.85-4.67 (m, 1 H), 4.60 (heptuplet, 1 H), 4.00-3.70 (dd, 2 H), 3.76-3.50 (m, 1 H), 1.95 (bs, 1 H), 1.80-1.55 (m, 2 H), 1.51 (d, 6 H), 1.03 (t, 3 H); IR (CH_2Cl_2) 3301, 2969, 1601, 1488, 1389, 1255, 762, 698 cm^{-1} ; API MS m/z = 431 [$\text{C}_{25}\text{H}_{30}\text{N}_6\text{O}+\text{H}$] $^+$.

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Example 58 - Preparation of Compound 74

Compound 72 (0.23 g, 0.60 mmol), *cis*-1,2-diaminocyclohexane (0.72 mL, 6.0 mmol), and ethanol (2 mL) were combined in a sealed tube and heated in an oil bath at 155 °C for 5 d. The ethanol was removed *in vacuo* and the crude reaction mixture was filtered through a silica plug. The reaction mixture was chromatographed on silica gel, the resulting orange solid was dissolved in CH₂Cl₂ and a portion of activated charcoal was added. The solution was filtered through a pad of celite and concentrated to give 74 as a yellow solid (0.04 g, 27%): ¹H NMR (300 MHz, CDCl₃) 7.59-7.31 (m, 10 H), 6.00 (s, 1 H), 5.09 (d, 1 H), 4.83 (s, 2 H), 4.68-4.62 (m, 1 H), 4.11 (s, 1 H), 3.70-3.65 (m, 2 H), 3.18-3.16 (m, 1 H), 2.02 (s, 2 H), 1.67-1.42 (m, 12 H); CI MS *m/z* = 456 [C₂₇H₃₃N₇+H]⁺.

Example 59 - Preparation of Compound 75

Compound 72 (0.17 g, 0.45 mmol), *trans*-1,4-diaminocyclohexane (0.53 g, 4.69 mmol), and EtOH (5 mL) were combined in a sealed tube and heated at 155 °C for 5 d. The EtOH was removed *in vacuo* and the crude mixture was subjected to flash chromatography on silica gel. Recrystallization from CHCl₃/MeOH gave 75 (5.8 mg) as an off-white crystalline solid: mp 110-112 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.31 (m, 10 H), 5.95 (s, 1 H), 4.88-4.78 (m, 2 H), 4.69-4.60 (m, 2 H), 3.88-3.78 (m, 1 H), 3.07-2.98 (m, 1 H), 2.26-2.10 (m, 4 H), 1.62-1.52 (m, 8 H), 1.29-1.15 (m, 4 H); CI MS *m/z* = 456 [C₂₇H₃₃N₇+H]⁺.

Example 60 - Preparation of Compound 76

Compound 75 (0.05 g, 0.11 mmol) was dissolved in CH₂Cl₂ and the solution cooled to 0 °C under an argon atmosphere. A catalytic amount of DMAP, triethylamine (50 L, 0.36 mmol), followed by the acetyl chloride (25 L, 0.36 mmol) were added to the reaction mixture. The solution was warmed to room temperature and washed with NaHCO₃ (5%), water, and brine. The solution was dried over Na₂SO₄ and concentrated. Purification by flash chromatography on silica gel gave 76 (0.028 g, 53%) as a pale yellow solid: mp 224-225 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.59-7.31 (m, 10 H), 5.93 (s, 1 H), 5.26 (d, 1 H), 4.81 (s, 2 H), 4.65-4.58 (m, 1 H).

3.78-3.75 (m, 2 H), 2.18-1.99 (m, 4 H), 1.95 (s, 3 H), 1.77 (s, 1 H), 1.53 (d, 6 H), 1.32-1.22 (m, 4 H); CI MS $m/z = 498$ [$C_{29}H_{35}N_7O+H$]⁺.

Example 61 - Preparation of Compound 77

5 Compound 72 (0.15 g, 0.40 mmol), *trans*-4-aminocyclohexanol hydrochloride (0.31 g, 1.99 mmol), Et₃N (0.11 mL, 0.8 mmol), and EtOH (5 mL) were combined and heated in a sealed tube at 155 °C for 4 d. Additional *trans*-4-aminocyclohexanol hydrochloride (0.34 g, 2.2 mmol) and triethylamine (0.60 mL, 4.3
10 mmol) were added and the heat was resumed at 155 °C overnight. The crude product was purified by flash column chromatography to give 77 (0.036 g, 20%) as an off-white solid: mp 196-200 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.30 (m, 10 H), 5.97 (s, 1 H), 4.83-4.81 (m, 2 H), 4.66-4.60 (m, 2 H), 3.82-3.77 (m, 1 H), 3.69-3.62 (m, 1 H), 2.17-2.13 (m, 2 H), 2.01-1.97 (m, 2 H), 1.68 (s, 1 H), 1.53 (d, 6 H), 1.49-1.20 (m,
15 4 H); CI MS $m/z = 457$ [$C_{27}H_{33}N_6O+H$]⁺.

Example 62 - Preparation of Compound 78

To compound 61 (0.12 g, 0.26 mmol), was added compound 16 (0.12
20 g, 0.33 mmol), and Pd(PPh₃)₄ (0.06 g, 0.056 mmol) and toluene (5 mL). The resulting mixture was degassed for 10 min with argon. The mixture was heated at 140 °C for 3 h. The cooled solution was diluted with saturated NaHCO₃ and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated to give a pale yellow oil which crystallized
25 upon standing at room temperature. The crude product was purified by column chromatography and concentrated to give a white solid. The solid was precipitated with acetonitrile, filtered, washed with ether and hexane to give 78 (0.02 g, 18%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (d, 1 H), 8.01 (d, 1 H), 7.93-7.83 (m, 2 H), 7.59-7.44 (m, 4 H), 7.34-7.29 (m, 1 H), 6.25 (s, 1 H), 4.70-4.60 (m, 2 H), 4.57-4.49 (m, 2
30 H), 3.65-3.52 (m, 1 H), 2.98-2.88 (m, 1 H), 1.98-1.90 (m, 4 H), 1.48 (d, 6 H), 1.42-1.18 (m, 6 H); CI MS $m/z = 457$ [$C_{26}H_{32}N_8+H$]⁺.

Example 63 - Preparation of Compound 78

To compound **24** (200 mg, 0.53 mmol) was added *trans*-1,4-diaminocyclohexane (2.00 g, 17 mmol) and EtOH (4 mL). The reagents were heated
5 in a sealed tube in an oil bath at 170 °C for 18 h. The mixture was cooled to 60 °C and partitioned between EtOAc and brine. The EtOAc layer was separated, washed with brine (3 x), dried with Na₂SO₄, and concentrated to give **78** (0.12 g, 50%): mp 135-138 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.03-7.82 (m, 2 H), 7.80-7.58 (m, 3 H), 7.57-7.30 (m, 3 H), 7.30-7.05 (m, 1 H), 6.20 (bs, 1 H), 5.95-4.73 (m, 2 H), 4.73-4.45
10 (m, 2 H), 3.90-3.60 (m, 1 H), 2.80-2.52 (m, 1 H), 2.25-1.80 (m, 4 H), 1.80-1.60 (bs, 3 H), 1.52 (d, 6 H), 1.38-1.05 (m, 4 H); IR (KBr) 3422, 2927, 1599, 1489, 1253, 779 cm⁻¹; API MS *m/z* = 457 [C₂₆H₃₂N₈+H]⁺.

Example 64 - Preparation of Compound 79

15 Compound **78** (50 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (2 mL) and stirred at room temperature. Pyridine (0.5 mL), Ac₂O (0.5 mL, 4.9 mmol), and DMAP (few crystals) were added to the reaction mixture and stirred for 2 h. The solution was diluted in CH₂Cl₂ and washed in 2N HCl. The HCl layer was
20 concentrated, CH₂Cl₂ was added and the aqueous phase neutralized with saturated NaHCO₃. The CH₂Cl₂ layer was separated, dried (MgSO₄), and concentrated to give **79** (0.03 g, 55%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.80 (m, 2 H), 7.81-7.57 (m, 2 H), 7.56-7.33 (m, 3 H), 7.30-7.05 (m, 2 H), 6.15-5.90 (bs, 1 H), 5.47-5.28 (m, 1 H), 4.96-4.72 (m, 2 H), 4.73-4.45 (m, 2 H), 2.25-1.82 (m, 4 H), 2.00 (s, 3
25 H), 1.54 (d, 6 H), 1.40-1.00 (m, 4 H); API MS *m/z* = 499 [C₂₈H₃₄N₈O+H]⁺.

Example 65 - Preparation of Compound 80

Compound **74** (0.02 g, 0.05 mmol) was dissolved in dry benzene (5
30 mL) and stirred under a blanket of argon. The solution was cooled in an ice bath and phenylisocyanate (25 L, 0.23 mmol) was added dropwise. The ice bath was removed and the mixture stirred at room temperature for 0.5 h. The solvent was evaporated *in vacuo* to give a yellow oil. The crude product was purified by flash column chromatography on silica gel to give **80** (0.008 g): ¹H NMR (300 MHz, CDCl₃) δ

7.53-7.30 (m, 10 H), 7.13-7.06 (m, 4 H), 6.98-6.88 (m, 1 H), 6.62 (s, 1 H), 6.02 (s, 1 H), 5.65 (s, 1 H), 5.02 (d, 1 H), 4.85-4.70 (m, 2 H), 4.60-4.52 (m, 1 H), 4.45-4.40 (m, 1 H), 4.36-4.22 (m, 2 H), 4.00 (s, 1 H), 1.91-1.60 (m, 6 H), 1.48-1.43 (m, 6 H).

5 **Example 66 - Preparation of Compound 82**

A mixture of 6-chloronicotinamide (2.96 g, 18.9 mmol), phenylboronic acid (2.54 g, 20.8 mmol), and Pd(PPh₃)₄ (643 mg, 0.565 mmol) in toluene (47 mL), ethanol (7 mL) and 2M aqueous sodium carbonate solution (21 mL, 43 mmol) was
10 stirred and heated at 90-100 °C under nitrogen for 16 h. The mixture was cooled to room temperature and filtered. The resulting solid was washed with water (2 x 20 mL) and dried *in vacuo*. To the dried solid was added methanol (50 mL). The mixture was stirred at reflux, cooled to room temperature, and filtered to give the product (90%) as a powder: mp 218-220 °C; ¹H NMR (500 Hz, DMSO-*d*₆) δ 9.23 (d,
15 J = 2.5 Hz, 1 H), 8.41 (dd, J₁ = 2.2 Hz, J₂ = 8.3 Hz, 1 H), 8.32 (s, 1 H), 8.27 (d, J = 7.1 Hz, 2 H), 8.20 (d, J = 8.5 Hz, 1 H), 7.74 (s, 1 H), 7.66-7.60 (m, 3 H).

Example 67 - Preparation of Compound 83

20 To NaBH₄ (0.19 g, 5 mmol) in 1,4-dioxane (4 mL) was added HOAc (0.3 g, 5 mmol) in 1,4-dioxane (2 mL) slowly while the flask was cooled with ice. Compound 82 (0.2 g, 1 mmol) was then added. The mixture was stirred at reflux at 100-110 °C for 4 h and the solvent was evaporated. To this mixture was added water (2 mL) slowly. The mixture was extracted with CH₂Cl₂ (4 x 10 mL), washed with
25 water (3 x 5 mL), dried with anhydrous sodium sulfate, concentrated, and purified by flash chromatography on silica gel to provide the product as a yellow liquid. This was triturated with ethanol (1 mL) to provide a white solid which was collected (60%) and dried: mp 97-99 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.60 (d, J = 2 Hz, 1 H), 7.97-7.95 (m, 2 H), 7.72-7.67 (m, 2 H), 7.47-7.37 (m, 3 H), 3.90 (s, 2 H), 1.77 (bs, 2 H).

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Example 68 - Preparation of Compound 84

A mixture of 2,6-dichloropurine (1.019 g, 1 mmol), amine 83 (0.39 g, 2.15 mmol) in ethanol (13 mL), and water (3 mL) was heated at 100-110 °C under

nitrogen for 24 h and then cooled to room temperature. The mixture was concentrated and water (5 mL) was added. A solid was filtered and washed with water (2 x 5 mL) and dried under vacuum to give the product (80%) as a yellow solid: mp 260 °C (dec); ¹H NMR (500 Hz, DMSO-*d*₆) δ 13.26 (s, 1 H), 8.79 (s, 1 H), 8.27 (s, 1 H), 8.16 (d, J = 7.1 Hz, 2 H), 8.34 (d, J = 7.3 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H), 7.63-7.52 (m, 3 H), 4.81 (s, 2 H).

Example 69 - Preparation of Compound 85

To a solution of compound **84** (0.34 g, 1 mmol) in DMSO (5 mL), was added potassium carbonate (0.7 g, 5 mmol) and 2-iodopropane (0.5 g, 3 mmol). The mixture was stirred at ambient temperature under nitrogen for 24 h and poured into ice water (30 mL). After filtration, the solid was washed with water (4 x 5 mL), dried under vacuum to give the crude product as a yellow solid. Flash column chromatography of the crude product on silica gel and recrystallization provided the pure product (63%) as ivory colored crystals: mp 138-139 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.70 (d, J = 1.5 Hz, 1 H), 7.97 (m, 2 H), 7.79 (dd, J₁ = 1.7 Hz, J₂ = 8.1 Hz, 1 H), 7.71 (s, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.48-7.39 (m, 3 H), 4.87 (s, 2 H), 4.80 (m, 1 H), 1.55 (d, J = 6.8 Hz, 6 H); CI MS *m/z* = 379 [C₂₀H₁₉ClN₆+H]⁺. Anal. Calcd. for C₂₀H₁₉ClN₆: C, 63.41; H, 5.05; N, 22.18. Found: C, 63.75; H, 5.09; N, 21.87.

Example 70 - Preparation of Compound 86

To compound **85** (0.1 g, 0.26 mmol) was added *trans*-1,4-diaminocyclohexane (1 g, 8.8 mmol) and EtOH (2 mL). The reaction mixture was heated in a sealed tube in an oil bath at 120 °C. The crude product was purified by column chromatography to give **86** (0.08 g, 67%): ¹H NMR (300 MHz, CDCl₃) δ 8.68 (d, 1 H), 7.83-7.97 (m, 2 H), 7.70-7.83 (m, 1 H), 7.55-7.73 (m, 1 H), 7.30-7.55 (m, 4 H), 6.35 (bs, 1 H), 4.72-4.95 (m, 2 H), 4.50-4.72 (m, 2 H), 3.63-3.85 (m, 1 H), 2.65-2.90 (m, 1 H), 2.37-2.63 (bs, 2 H), 1.80-2.20 (dd, 4 H), 1.53 (d, 6 H), 0.72-1.42 (m, 4 H); API MS *m/z* = 457 [C₂₆H₂₂N₈+H]⁺.

Example 71 - Preparation of Compound 87

Compound **86** (0.08 g, 0.18 mmol) was stirred at room temperature in CH₂Cl₂ (3 mL). Pyridine (100 mg, 0.82 mmol) was added followed by Ac₂O (100 mg, 0.98 mmol) and DMAP (few crystals). After 2 h, more CH₂Cl₂ (3 mL) was added and the mixture was washed carefully with 2N HCl (10 drops), and saturated NaHCO₃. After separation of the CH₂Cl₂ layer, the organic phase was then dried with Na₂SO₄ and concentrated to give **87** (80 mg, 92%): ¹H NMR (300 MHz, CDCl₃) δ 8.72 (s, 1 H), 8.30-7.03 (m, 9 H), 5.75-5.38 (m, 1 H), 5.02 (bs, 1 H), 4.83 (bs, 2 H), 4.72-4.40 (m, 1 H), 3.73 (bs, 2 H), 2.52-1.83 (m, 4 H), 1.98 (s, 3 H), 1.52 (d, 6 H), 1.50-1.00 (m, 4 H); API MS *m/z* = 499 [C₂₈H₃₄N₈O+H]⁺.

Example 72 - Preparation of Compound 88

Compound **85** (0.05 g, 0.13 mmol) and (*R*)-(-)-2-amino-1-butanol (0.50 g, 5.6 mmol) were combined in a sealed tube and heated in an oil bath at 190 °C for 2 h then cooled to room temperature. The mixture was partitioned between EtOAc and brine, washed with brine (3 x), dried with Na₂SO₄, and concentrated. The mixture was allowed to stand over the weekend and then purified by column chromatography on SiO₂ to give **88** (0.01 g, 17%) as a foam: ¹H NMR (300 MHz, CDCl₃) δ 8.70 (s, 1 H), 8.05-7.82 (m, 2 H), 7.82-7.55 (m, 2 H), 7.57-7.30 (m, 4 H), 6.55 (bs, 1 H), 5.00-4.88 (s, 1 H), 4.78 (s, 2 H), 4.60 (heptuplet, 1 H), 3.98-3.83 (m, 1 H), 3.84-3.70 (m, 1 H), 3.70-3.50 (m, 1 H), 2.90 (bs, 1 H), 1.75-1.55 (m, 2 H), 1.53 (d, 6 H), 1.00 (t, 3 H); API MS *m/z* = 432 [C₂₄H₂₉N₇O+H]⁺.

Example 73 - Preparation of Compound 89

A mixture of 6-chloronicotinamide (2.5 g, 16 mmol), crude 2-trimethylstannylpyridine (5.8 g, 24 mmol), and PdCl₂(PPh₃)₂ (560 mg, 0.8 mmol) in DMF (35 mL) was heated at 150-160 °C in a pressure tube for 17 h. The DMF was distilled off under reduced pressure and the residue was extracted with ethyl acetate (6 x 30 mL) and concentrated. The residue was treated with methanol (15 mL) and a solid separated which was filtered and dried to give the product (40%) as a powder: mp 237-240 °C: ¹H NMR (500 Hz, DMSO-*d*₆) 9.22 (d, *J* = 2.2 Hz, 1 H), 8.83 (m, 1 H)

8.57-8.53 (m, 2 H), 8.48-8.46 (m, 1 H), 8.38 (s, 1 H), 8.11-8.07 (m, 1 H), 7.78 (s, 1 H), 7.63-7.60 (m, 1 H).

Example 74 - Preparation of Compound 90

5 To NaBH₄ (0.2 g, 5 mmol) in 1,4-dioxane (4 mL) was added HOAc (0.29 g, 5 mmol) in 1,4-dioxane (2 mL) slowly while the flask was cooled with ice. Compound **89** (0.199 g, 1 mmol) was then added. The mixture was stirred at reflux at 100-110 °C for 4 h and the solvent was evaporated. To this mixture was added water
10 (2 mL) slowly. The mixture was extracted with CH₂Cl₂ (4 x 10 mL), washed with water (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, concentrated, and purified by flash chromatography on silica gel to provide the product as a yellow liquid. This was triturated with ethanol (1 mL) and a white solid (32%) was collected and dried: mp 109-112 °C; ¹H NMR (500 Hz, CDCl₃) δ 8.63 (m, 1 H), 8.58 (s, 1 H),
15 8.32 (m, 2 H), 7.77 (m, 2 H), 7.25 (m, 1 H), 3.91 (s, 2 H), 1.94 (s, 2 H).

Example 75 - Preparation of Compound 91

A mixture of 2,6-dichloropurine (**1**, 0.2 g, 1 mmol), compound **90** (0.4
20 g, 2.2 mmol) in ethanol (13 mL), and water (3 mL) was heated at 100-110 °C under nitrogen for 24 h and then cooled to room temperature. The mixture was concentrated and water (5 mL) was added. A solid was filtered and washed with water (2 x 5 mL) and dried under vacuum to give the product (83%) as a yellow solid: mp 248 °C (dec); ¹H NMR (500 Hz, DMSO-*d*₆) δ 13.27 (s, 1 H), 8.81 (s, 1 H), 8.78 (d, J = 4.1
25 Hz, 1 H), 8.47 (m, 2 H), 8.28 (s, 1 H), 8.06-8.01 (m, 2 H), 7.50 (m, 1 H), 4.84 (s, 2 H).

Example 76 - Preparation of Compound 92

To the solution of compound **91** (0.35 g, 1 mmol) in DMSO (5 mL),
30 added potassium carbonate (0.68 g, 5 mmol) and 2-iodopropane (0.49 g, 3 mmol). The mixture was stirred at ambient temperature under nitrogen for 24 h and poured into ice water (30 mL). After filtration, the solid was washed with water (4 x 5 mL), dried under vacuum to give the crude product as a yellow solid. Flash column chromatography of the crude product on silica gel and recrystallization provided the

pure product (64%) as white crystals: mp 150-151 °C: ¹H NMR (500 Hz, CDCl₃) δ 8.71 (d, J = 1.9 Hz, 1 H), 8.67 (m, 1 H), 8.38-8.36 (m, 2 H), 7.86-7.79 (m, 2 H), 7.75 (s, 1 H), 7.30 (m, 1 H), 4.91 (s, 2 H), 4.82 (m, 1 H), 1.57 (d, J = 6.8 Hz, 6 H); CI MS $m/z = 380$ [C₁₉H₁₈ClN₇+H]⁺. Anal. Calcd. for C₁₉H₁₈ClN₇: C, 60.08; H, 4.78; N, 25.81. Found: C, 59.76; H, 4.72; N, 25.57.

Example 77 - Preparation of Compound 93

Compound **92** (150 mg, 0.39 mmol), *trans*-1,4-diaminocyclohexane (1.50 g, 13.1 mmol), and EtOH (30 mL) were heated to 120 °C for 26 h in a sealed tube. The mixture was cooled, additional EtOAc was added, washed with brine, dried over Na₂SO₄, and concentrated to give **93** (170 mg, 94%) as a waxy solid: ¹H NMR (300 MHz, CDCl₃) δ 8.77-8.60 (m, 1 H), 8.44-8.27 (m, 2 H), 7.90-7.75 (m, 2 H), 7.50 (s, 1 H), 7.36-7.22 (m, 2 H), 6.27 (bs, 1 H), 4.96-4.73 (m, 2 H), 4.73-4.52 (m, 2 H), 3.84-3.60 (m, 1 H), 2.80-2.57 (m, 1 H), 2.22-2.00 (m, 2 H), 2.00-1.67 (m, 5 H), 1.54 (d, 6 H), 1.38-1.05 (m, 4 H); API MS $m/z = 458$ [C₂₅H₃₁N₉+H]⁺.

Example 78 - Preparation of Compound 94

Compound **93** (0.15 g, 0.33 mmol) was dissolved in CH₂Cl₂ (6 mL) and then pyridine (0.200 g, 1.64 mmol) followed by Ac₂O (0.200 g, 1.96 mmol) and DMAP (few crystals) were added. The reaction mixture was stirred for 2 h, washed with 2N HCl and NaHCO₃, extracted with CH₂Cl₂, dried with Na₂SO₄, and concentrated to give **94** (0.17 g, 69%) as a solid: mp 141-145 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.80-8.63 (m, 1 H), 8.45-8.25 (t, 2 H), 7.95-7.73 (m, 1 H), 7.52 (s, 1 H), 7.35-7.20 (m, 2 H), 6.20 (bs, 1 H), 5.50-5.30 (m, 1 H), 4.98-4.75 (m, 2 H), 4.75-4.50 (m, 2 H), 3.84-3.60 (m, 2 H), 2.27-1.87 (m, 4 H), 2.00 (s, 3 H), 1.52 (d, 6 H), 1.40-1.10 (m, 4 H); API MS $m/z = 499$ [C₂₇H₃₃N₉O+H]⁺.

Example 79 - Preparation of Compound 95

DME (3 mL), tris(dibenzylideneacetone)dipalladium (0.01 g, 0.01 mmol), and PPh₃ (0.04 g, 0.15 mmol) were added to a round bottomed flask equipped with a condensor and maintained under an argon atmosphere. To the solution was

added compound **11** (0.13 g, 0.25 mmol). 3-Fluorobenzene boronic acid (0.123 g, 0.9 mmol) was dissolved in a solution of 2M Na₂CO₃ (0.6 mL) and DME (1 mL), and added to the reaction mixture. The mixture was stirred under argon and refluxed for 19 h then stirred at room temperature for 22 h. The reaction mixture was diluted with H₂O, extracted with CH₂Cl₂, washed with brine. The organic layer was dried over Na₂SO₄ and evaporated. The reaction mixture was purified twice by column chromatography and dried under high vacuum to give a white solid (17 mg, 14%): ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.32 (m, 8 H), 7.08-6.99 (m, 1 H), 5.86 (br, 1 H), 4.83 (d, 2 H), 4.71-4.56 (m, 1 H), 3.77 (br, 2 H), 2.70 (br, 1 H), 2.12 (d, 1 H), 1.88 (d, 1 H), 1.51 (d, 6 H), 1.22 (d, 5 H), 0.94-0.70 (m, 3 H); API MS *m/z* = 474 [C₂₇H₃₂FN₇+H]⁺.

Example 80 - Preparation of Compound 96

A stock solution of acetic anhydride was made by mixing CH₂Cl₂ (16 mL), pyridine (4 mL), and Ac₂O (0.16 mL). To this stock solution (1.5 mL) was added compound **95** (0.01 g, 0.02 mmol) followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 26 h. The reaction mixture was then diluted with CH₂Cl₂, washed with 2N HCl until the aqueous layer was acidic, washed with NaHCO₃, dried over MgSO₄, evaporated, and dried *in vacuo* for 15 h to give a white solid (11 mg, 92%): ¹H NMR (300 MHz, CDCl₃) δ 8.65 (br, 1 H), 7.77-7.17 (m, 8 H), 7.11-6.99 (m, 1 H), 5.14 (br, 2 H), 4.90 (br, 1 H), 4.69 (br, 1 H), 3.78 (br, 2 H), 2.09 (br, 3 H), 1.94 (s, 2 H), 1.57 (d, 6 H), 1.42 (br, 4 H), 1.24 (s, 2 H), 0.94-0.76 (m, 1 H); CI MS *m/z* = 516 [C₂₉H₃₄FN₇O+H]⁺.

Example 81 - Preparation of Compound 97

A stock solution of acetic anhydride was made by mixing CH₂Cl₂ (16 mL), pyridine (4 mL), and Ac₂O (0.16 mL). To this stock solution (1.5 mL) was added compound **13** (0.01 g, 0.02 mmol) followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was then diluted with CH₂Cl₂, washed with 2N HCl until it was acidic, washed with NaHCO₃, dried over MgSO₄, and evaporated to give a white solid (8 mg,

89%): ^1H NMR (300 MHz, CDCl_3) δ 8.78 (d, 1 H), 8.44 (t, 1 H), 7.95 (t, 2 H), 7.69-7.45 (m, 5 H), 5.30 (br, 2 H), 4.84 (br, 1 H), 4.68 (br, 1 H), 3.78 (br, 2 H), 2.39 (s, 3 H), 2.10 (br, 4 H), 1.96 (s, 2 H), 1.57 (br, 10 H), 1.25 (s, 2 H), 0.88 (br, 1 H); API MS $m/z = 512 [\text{C}_{30}\text{H}_{37}\text{N}_7\text{O}+\text{H}]^+$.

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Example 82 - Preparation of Compound 98

DME (3 mL), tris(dibenzylideneacetone)dipalladium (0.01 g, 0.01 mmol), and PPh_3 (0.04 g, 0.15 mmol) were added to a round bottom flask equipped with condensor and maintained under an argon atmosphere. Iodide **11** (0.13 g, 0.26 mmol), and 3-chlorobenzene boronic acid (0.15 g, 0.93 mmol) was dissolved in 2M Na_2CO_3 (0.6 mL) and DME (1 mL). This was then added to the reaction mixture and refluxed for 19.5 h then stirred at room temperature for 30 h. The reaction mixture was then diluted with H_2O , extracted with CH_2Cl_2 , washed with brine, dried over Na_2SO_4 , filtered, and evaporated. The reaction mixture was purified by column chromatography (3 x) and evaporated. The product was triturated in hexanes, filtered, and dried *in vacuo* for 1 h to give a white solid (16 mg): ^1H NMR (300 MHz, CDCl_3) δ 7.56-7.38 (m, 9 H), 6.01 (br, 1 H), 4.80 (d, 2 H), 4.71-4.62 (m, 1 H), 3.77 (br, 2 H), 2.73 (br, 1 H), 2.19-2.04 (m, 1 H), 1.94-1.85 (m, 1 H), 1.51 (d, 6 H), 1.24 (d, 5 H), 0.91-1.76 (m, 3 H); API MS $m/z = 490 [\text{C}_{27}\text{H}_{32}\text{ClN}_7+\text{H}]^+$.

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Example 83 - Preparation of Compound 99

A stock solution of acetic anhydride was made by mixing CH_2Cl_2 (16 mL), pyridine (4 mL), and Ac_2O (0.16 mL). To this solution (1.5 mL) was added compound **98** (0.01 g, 0.02 mmol), followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 , washed with 2N HCl until the aqueous layer was acidic, washed with NaHCO_3 , dried over MgSO_4 , filtered, and evaporated to give a white solid (0.01 g, 83%): ^1H NMR (300 MHz, CDCl_3) δ 7.65-7.35 (m, 8 H), 7.26-7.14 (m, 1 H), 5.23 (br, 1 H), 4.66 (br, 1 H), 3.78 (br, 2 H), 2.18-2.00 (m, 4 H), 1.94 (s, 3 H), 1.54 (d, 6 H), 1.24 (s, 5 H), 0.94-0.69 (m, 3 H); API MS $m/z = 532 [\text{C}_{29}\text{H}_{34}\text{ClN}_7\text{O}+\text{H}]^+$.

30

Example 84 - Preparation of Compound 100

A stock solution of acetic anhydride was made by mixing CH₂Cl₂ (16 mL), pyridine (4 mL), and Ac₂O (0.16 mL). To compound **14** (0.02 g, 0.03 mmol) was added this solution (2 mL), followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was diluted with CH₂Cl₂, washed with 2N HCl until the aqueous layer was acidic, washed with NaHCO₃, filtered, and evaporated to give a white solid (8 mg, 44%): ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.32 (m, 7 H), 7.26-7.14 (m, 1 H), 5.96 (br, 1 H), 5.23 (d, 1 H), 4.84 (br, 2 H), 4.69-4.54 (m, 1 H), 3.75 (br, 1 H), 2.21-2.12 (m, 1 H), 2.09-1.96 (m, 1 H), 1.97 (s, 3 H), 1.54 (d, 6 H), 1.36-1.15 (m, 5 H), 0.85 (br, 3 H); API MS *m/z* = 550 [C₂₉H₃₃ClFN₇O+H]⁺.

Example 85 - Preparation of Compound 101

DME (3 mL), tris(dibenzylideneacetone)dipalladium (0.01 g, 0.01 mmol), and PPh₃ (0.04 g, 0.15 mmol) were added to a round bottomed flask equipped with a condensor and maintained under an argon atmosphere. Compound **10** (0.13 g, 0.26 mmol) and 4-fluorobenzene boronic acid (0.13 g, 0.95 mmol) was dissolved in 2M Na₂CO₃ (0.6 mL) and DME (1 mL). This was then added to the reaction mixture and refluxed for 19 h then stirred at room temperature for 72 h. The reaction mixture was then diluted with H₂O, extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, filtered, and evaporated. The reaction mixture was purified by column chromatography on silica gel to give a white solid (17 mg, 14%): ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.38 (m, 8 H), 7.11 (t, 1 H), 5.81 (br, 1 H), 4.81 (d, 2 H), 4.69-4.57 (m, 1 H), 3.78 (br, 2 H), 2.69 (br, 1 H), 2.12 (br, 1 H), 1.88 (br, 1 H), 1.54 (d, 6 H), 1.33-1.12 (m, 5 H), 0.85 (br, 3 H); API MS *m/z* = 474 [C₂₇H₃₂FN₇+H]⁺.

Example 86 - Preparation of Compound 102

A stock solution of acetic anhydride was made by mixing CH₂Cl₂ (16 mL), pyridine (4 mL), and Ac₂O (0.16 mL). To the solution (1.4 mL) was added compound **101** (0.01 g, 0.02 mmol), followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 2.5 h. The reaction mixture was

diluted with CH_2Cl_2 , washed with 2N HCl until the aqueous layer was acidic, and washed with saturated NaHCO_3 . The organic layer was dried over MgSO_4 and evaporated to give a product (3 mg). The NaHCO_3 layer was further extracted with EtOAc (2 x), the organic layers were combined, dried over MgSO_4 , evaporated to give product **102** (2 mg). The products were combined using EtOAc, evaporated, and dried *in vacuo* for 15 h to give product **102** (5 mg, 50%): ^1H NMR (300 MHz, CDCl_3) δ 7.71-7.08 (m, 9 H), 5.29 (br, 2 H), 4.84 (br, 1 H), 4.66 (br, 1 H), 3.78 (br, 2 H), 2.09 (br, 4 H), 1.97 (s, 1 H), 1.57 (br, 3 H), 1.24 (d, 6 H), 0.87 (br, 5 H); API MS $m/z = 516$ [$\text{C}_{29}\text{H}_{34}\text{FN}_7\text{O}+\text{H}$] $^+$.

10

Example 87 - Preparation of Compound 103

Compound **30** (0.10 g, 0.27 mmol) and *trans*-1,4-diaminocyclohexane (0.48 g, 4.2 mmol) were combined with EtOH (2 mL) in a sealed tube and heated at 190 °C for 24 h, and then stirred at room temperature for 46 h. The reaction mixture was purified by column chromatography and dried *in vacuo* to give **103** as a white solid (0.10 g, 81%): ^1H NMR (300 MHz, CDCl_3) δ 8.83 (d, 1 H), 8.58 (t, 1 H), 7.87-7.83 (m, 1 H), 7.55-7.47 (m, 5 H), 7.38-7.33 (m, 1 H), 5.96 (br, 1 H), 4.82 (d, 2 H), 4.68-4.59 (m, 1 H), 3.75 (br, 2 H), 2.69 (br, 1 H), 2.14 (d, 2 H), 1.86 (d, 2 H), 1.54 (d, 6 H), 1.31-1.18 (m, 5 H); API MS $m/z = 457$ [$\text{C}_{26}\text{H}_{32}\text{N}_8+\text{H}$] $^+$.

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Example 88 - Preparation of Compound 104

A stock solution of acetic anhydride was made by mixing CH_2Cl_2 (16 mL), pyridine (4 mL), and Ac_2O (0.16 mL). To the solution (3.1 mL) was added compound **103** (0.02 g, 0.04 mmol), followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 2.5 h. The reaction mixture was evaporated, dried *in vacuo* for 19 h, and purified by column chromatography to give a white solid (0.02 g): ^1H NMR (300 MHz, CDCl_3) δ 8.83 (d, 1 H), 8.59 (t, 1 H), 7.85 (d, 1 H), 7.55-7.47 (m, 5 H), 7.38-7.34 (m, 1 H), 5.89 (br, 1 H), 5.25 (d, 2 H), 4.85 (br, 1 H), 4.66-4.61 (m, 1 H), 3.77 (br, 2 H), 2.15 (br, 2 H), 2.05 (br, 2 H), 1.97 (s, 2 H), 1.54 (d, 6 H), 1.33-1.25 (m, 5 H), 0.88 (br, 1 H); API MS $m/z = 499$ [$\text{C}_{28}\text{H}_{34}\text{N}_8\text{O}+\text{H}$] $^+$.

30

Example 89 - Preparation of Compound 106

Compound **72** (0.30 g, 0.80 mmol) and compound **105** (1.15 g, 6.50 mmol) (Gardiner, J.M., et al. Tetrahedron, 42(11):515 (1995), which is hereby incorporated by reference, were combined with EtOH (7 mL) and allowed to reflux for 23 h. Triethylamine (1 mL) was added and the reaction was refluxed further for another 21 h. The reaction mixture was then transferred to a sealed tube and EtOH (3 mL) was added. The reaction mixture was heated further at 100 °C for 3 h. The mixture was purified by column chromatography to give **105** (0.13 g): ¹H NMR (300 MHz, CDCl₃) δ 7.57-7.26 (m, 10 H), 5.58 (br, 1 H), 5.10 (br, 1 H), 4.83 (br, 1 H), 4.69-4.62 (m, 2 H), 3.36-2.91 (m, 5 H), 2.82-2.65 (m, 2 H), 1.53 (d, 2 H), 1.44 (s, 9 H), 1.25 (d, 1 H), 1.13 (d, 3 H); CI MS *m/z* = 416 [C₂₉H₃₉N₇O-Boc+H]⁺.

Example 90 - Preparation of Compound 107

To compound **106** (0.10 g, 0.18 mmol) was added Et₂O (2 mL), CH₂Cl₂ (1 mL) and MeOH (1 mL). During 16 h HCl/ether (1M, 5 mL) was added while stirring. The resulting precipitate was collected by filtration and dried *in vacuo* for 30 min to provide **106** as an off-white solid (60 mg, 81%): ¹H NMR (300 MHz, DMSO) δ 8.48 (br, 2 H), 8.15 (br, 1 H), 7.67-7.27 (m, 10 H), 4.79 (br, 1 H), 3.60-3.42 (m, 3 H), 3.18-3.06 (m, 2 H), 3.03-2.91 (m, 2 H), 1.52 (d, 2 H), 1.27 (d, 6 H); CI MS *m/z* = 416 [C₂₄H₂₉N₇+H]⁺.

Example 91 - Preparation of Compound 108

A stock solution of acetic anhydride was made by mixing CH₂Cl₂ (16 mL), pyridine (4 mL), and Ac₂O (0.16 mL). To this solution (5.6 mL) was added compound **107** (0.04 g, 0.09 mmol), followed by DMAP (few crystals). The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with CH₂Cl₂, washed with 2N HCl until acidic, the organic layer was washed with NaHCO₃, dried over MgSO₄, filtered, and evaporated to give a white solid (16 mg). The product was purified by column chromatography to provide **108** as a white solid (0.01 g, 18%): ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.43 (m, 10 H), 6.60 (br, 1

H). 5.91 (br. 1 H), 5.04 (t. 1 H), 4.84 (br. 2 H), 4.72-4.59 (m. 1 H), 4.10-4.02 (m. 1 H), 3.59-3.47 (m. 2 H), 1.80 (s. 3 H), 1.57 (d. 6 H), 1.19 (d. 3 H); CI MS m/z = 458 $[\text{C}_{26}\text{H}_{31}\text{N}_7\text{O}+\text{H}]^+$.

5 **Example 92 - Preparation of Compound 109**

Compound **61** (1.0 g, 2.18 mmol), 3-chlorophenylboronic acid (1.3 g, 8.16 mmol), PPh_3 (0.3 g, 1.26 mmol), 2M Na_2CO_3 (5.0 mL), and DME (54 mL) were added to a three-necked round-bottomed flask. The mixture was degassed with argon and heated to reflux for 40 min, cooled to room temperature, and then $\text{Pd}_2(\text{dba})_3$ (0.08 g, 0.08 mmol) was added. The reaction mixture was heated at reflux for 7 h. 3-Chlorophenylboronic acid (0.6 g) and $\text{Pd}_2(\text{dba})_3$ (0.08 g) was then added and reflux continued for 12 h. The reaction mixture was cooled to room temperature, diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography and concentrated *in vacuo* to obtain compound **109** (950 mg, 89%): mp 178-181 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.56 (s, 1 H), 7.42-7.54 (m, 6 H), 7.26-7.35 (m, 2 H), 6.08 (bs, 1 H), 4.81 (bs, 2 H), 4.59-4.64 (m, 2 H), 3.75-3.81 (m, 1 H), 2.65-2.72 (m, 1 H), 2.12 (d, 2 H), 1.88 (d, 2 H), 1.53 (d, 6 H), 1.18-1.27 (m, 4 H); CI MS m/z = 490 $[\text{C}_{27}\text{H}_{32}\text{ClN}_7+\text{H}]^+$.

Example 93 - Preparation of Compound 110

Compound **109** (500 mg, 1.02 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL), cooled with an ice-water bath, followed by the addition of DMAP (12.2 mg, 0.1 mmol), pyridine (124 μL , 1.53 mmol), and Ac_2O (106 μL , 1.12 mmol). The reaction mixture was stirred for 30 min at 0 °C an ice-water bath then stirred another 2 h at room temperature. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica gel. After removal of the solvent, the residue was dried *in vacuo* to give **110** (339 mg, 63%): mp 198-200 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.57 (s, 1 H), 7.39-7.53 (m, 6 H), 7.27-7.37 (m, 2 H), 6.31 (bs, 1 H), 5.28 (d, 1 H), 4.78 (bs, 2 H), 4.70 (d, 1 H), 4.58-

4.67 (m, 1 H), 3.72-3.83 (m, 1 H), 2.18 (d, 2 H), 2.00 (d, 2 H), 1.90 (s, 3 H), 1.51 (d, 6 H), 1.18-1.31 (m, 4 H); CI MS m/z = 532 [$C_{29}H_{34}ClN_7O+H$]⁻.

Example 94 - Preparation of Compound 111

5 Compound **61** (1.0 g, 2.18 mmol), 2-thiopheneboronic acid (1.0 g, 8.16 mmol), PPh₃ (0.3 g, 1.26 mmol), 2M Na₂CO₃ (5.0 mL), Pd₂(dba)₃ (0.08 g, 0.08 mmol), and DME (54 mL) were added to a round-bottomed flask and purged with argon. The reaction mixture was heated at reflux for 24 h. 2-Thiopheneboronic acid
10 (0.5 g), Pd₂(dba)₃ (0.1 g), and 2M Na₂CO₃ (2 mL) were added and heated to reflux for another 24 h. The reaction mixture was cooled to room temperature, diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The organic phase was washed with H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was repeatedly chromatographed on silica gel to obtain **111** (574
15 mg, 59%); mp 109-110 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, 2 H), 7.54 (s, 1 H), 7.46 (d, 2 H), 7.24-7.37 (m, 2 H), 7.06 (t, 1 H), 6.04 (bs, 1 H), 4.78 (bs, 2 H), 4.59-4.69 (m, 2 H), 3.75-3.81 (m, 1 H), 2.67-2.74 (m, 1 H), 2.14 (d, 2 H), 1.87 (d, 2 H), 1.52 (d, 6 H), 1.17-1.29 (m, 4 H); CI MS m/z = 462 [$C_{25}H_{31}N_7S+H$]⁺.

Example 95 - Preparation of Compound 112

20 Compound **111** (410.0 mg, 0.89 mmol) was dissolved in anhydrous CH₂Cl₂ (30 mL) and purged with N₂ and cooled with an ice-water bath. Pyridine (108 mg, 1.34 mmol) and DMAP (10.9 mg, 0.09 mmol) followed by Ac₂O (92 μL, 0.98
25 mmol) were added slowly. The reaction mixture was stirred for 30 min in an ice-water bath followed by 2 h at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel to give **112** (325 mg, 73%); mp 237-244 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, 2 H), 7.50 (s, 1 H), 7.36 (d, 2 H), 7.24-7.37 (m, 2 H), 7.08 (t, 1 H), 6.06 (bs, 1 H), 5.34 (s, 1 H),
30 4.78 (bs, 2 H), 4.58-4.70 (m, 2 H), 3.78 (bs, 2 H), 2.17 (d, 2 H), 2.04 (d, 2 H), 1.96 (s, 3 H), 1.56 (d, 6 H), 1.18-1.32 (m, 4 H); CI MS m/z = 504 [$C_{27}H_{33}N_7OS+H$]⁺.

Example 96 - Preparation of Compound 113

Compound **12** (600 mg, 1.30 mmol) was dissolved in anhydrous CH₂Cl₂ (40 mL), purged with N₂, and cooled to 0 °C followed by an addition of DMAP (15.9 mg, 0.13 mmol), pyridine (165.3 mg, 1.95 mmol), and Ac₂O (135 mg, 1.43 mmol). The mixture was stirred 30 min at 0 °C then 2 h at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel to give **113** (495 mg, 76%): mp 248-253 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, 2 H), 7.46 (s, 1 H), 7.35-7.41 (m, 5 H), 6.13 (bs, 1 H), 5.28 (d, 1 H), 4.78 (br, 2 H), 4.61-4.63 (m, 2 H), 3.75 (bs, 2 H), 2.14 (d, 2 H), 1.97 (d, 2 H), 1.95 (s, 3 H), 1.52 (d, 6 H), 1.15-1.37 (m, 4 H); CI MS *m/z* = 504 [C₂₇H₃₃N₇OS+H]⁺.

Example 97 - Preparation of Compound 114

To compound **61** (1.0 g, 2.18 mmol) was added PPh₃ (330 mg, 1.26 mmol), 2M Na₂CO₃ (5 mL), DME (54 mL), and 4-carboxyphenylboronic acid (1.0 g, 6.03 mmol). The mixture was purged with N₂ for 45 min then Pd₂(dba)₃ (366 mg, 0.4 mmol) was added and the mixture was heated at reflux for 3 d. The reaction mixture was diluted with H₂O (100 mL). The aqueous layer was separated, and washed with CH₂Cl₂ (3 x 40 mL). The aqueous layer was adjusted the pH to 5.8 by using 1N HCl. Some precipitate appeared. The mixture was stored in a freezer overnight. The precipitate was collected and dried to obtain **114** (450 mg, 41%): mp 246-249 °C (dec.); ¹H NMR (500 MHz, CD₃OD+NaOD) δ 7.84 (s, 2 H), 7.64 (s, 1 H), 7.54-7.63 (m, 4 H), 7.39 (s, 2 H), 6.08 (bs, 1 H), 4.85 (bs, 2 H), 4.73 (s, 1 H), 3.76 (m, 1 H), 2.74 (m, 1 H), 1.99 (s, 2 H), 1.88 (s, 2 H), 1.63 (d, 6 H), 1.21-1.36 (m, 4 H); CI MS *m/z* = 500 [C₂₈H₃₃N₇O₂+H]⁺.

Example 98 - Preparation of Compound 115

To a cooled MeOH (20 mL) solution was slowly added TMSCl (253 μL, 2.0 mmol). The solution was stirred 20 min, followed by the addition of **114** (100 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was cooled with an ice-water bath then Et₃N (557 mL) was added. The mixture was concentrated *in vacuo*, to provide the crude product, which was

washed with water (2 x 20 mL). The residue was purified by chromatography on a silica gel. After removal of the solvent and drying *in vacuo*, the residue was dissolved in MeOH (5 mL), followed by the addition of ether (10 mL). The precipitate was collected and dried to provide **115** (75 mg, 73%): mp 194-197 °C: ¹H NMR (500 MHz, CD₃OD) δ 8.07 (d, 2 H), 7.80 (s, 1 H), 7.72 (d, 2 H), 7.63 (d, 2 H), 7.46 (d, 2 H), 4.63-4.79 (m, 1 H), 3.91 (s, 3 H), 3.65-3.77 (m, 1 H), 3.07 (bs, 1 H), 2.12 (d, 2 H), 2.01 (d, 2 H), 1.55 (d, 6 H), 1.29-1.49 (m, 4 H); API MS *m/z* = 514 [C₂₉H₃₅N₇O₂+H]⁺.

Example 99 - Preparation of Compound 117

To a suspension of compound **114** (250 mg, 0.50 mmol), pyridine (60 μL, 0.75 mmol), and DMAP (6.1 mg, 0.05 mmol) in H₂O-dioxane (2:1, 40 mL) was added Ac₂O (57 μL, 0.60 mmol). After stirring 4 h at room temperature, K₂CO₃ (100 mg) was added followed by additional Ac₂O (100 μL). The reaction mixture was stirred 2 h at room temperature. Water (50 mL) was added and the pH was adjusted to 5. The precipitate was collected, washed with water and ether, and dried *in vacuo*. The precipitate (200 mg) was added to a solution of TMSCl (500 μL, 3.94 mmol) in MeOH (25 mL). The reaction mixture was stirred 24 h at room temperature. The mixture was concentrated *in vacuo*. The product was purified by silical gel chromatography to provide **117** (145 mg, 52%): mp 247-250 °C: ¹H NMR (500 MHz, CDCl₃) δ 8.09 (d, 2 H), 7.64 (d, 2 H), 7.58 (d, 2 H), 7.49 (s, 1 H), 7.45 (d, 2 H), 5.91 (bs, 1 H), 5.18 (d, 1 H), 4.83 (bs, 2 H), 4.61-4.68 (m, 2 H), 3.93 (s, 3 H), 3.67-3.78 (m, 2 H), 3.07 (bs, 1 H), 2.16 (d, 2 H), 2.02 (d, 2 H), 1.95 (s, 3 H), 1.54 (d, 6 H), 1.23-1.32 (m, 4 H); API MS *m/z* = 556 [C₃₁H₃₇N₇O₃+H]⁺.

Example 100 - Preparation of Compound 116

To a solution of compound **117** (90 mg, 0.16 mmol) in MeOH-H₂O (6:1, 23 mL) was added KOH (11 mg, 0.19 mmol) in 5 mL MeOH. The reaction mixture was refluxed for 24 h. After removal of the solvent the residue was dissolved in 15 mL of water and washed with CH₂Cl₂. The aqueous layer was separated and adjusted pH to 4.5 by using 1N HCl. The precipitate was collected and dried to obtain **116** (60 mg, 68%): mp 344-347 °C: ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.21 (bs, 1

H). 8.14 (d, 2 H), 7.64-7.88 (m, 6 H), 7.47 (d, 2 H), 6.06 (bs, 1 H), 5.18 (d, 1 H), 4.85 (bs, 2 H), 4.51-4.66 (m, 1 H), 3.62 (bs, 1 H), 3.46 (bs, 1 H), 1.89 (bs, 2 H), 1.77 (bs, 5 H), 1.95 (s, 3 H), 1.47 (d, 6 H), 1.23-1.36 (m, 4 H); API MS m/z = 542 $[C_{30}H_{35}N_7O_3+H]^+$.

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Example 101 - Preparation of Compound 118

Compound **61** (1.0 g, 2.18 mmol), 3-carboxyphenylboronic acid (1.0 g, 6.03 mmol), 2N Na_2CO_3 (5 mL), and DME/EtOH (50 mL) were mixed together and
10 degassed with N_2 for 1 h. $Pd_2(dba)_3$ (366.0 mg, 0.4 mmol) and PPh_3 (330.0 mg, 1.26 mmol) were added and the reaction mixture was heated to reflux for 48 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (50 mL), and extracted with aqueous 5% Na_2CO_3 (3 x 30 mL). The combined washes were extracted with CH_2Cl_2 (3 x 30 mL) and ether (40 mL). The aqueous phase was
15 neutralized to a pH of 5.8 using 1N HCl and kept in a freezer for 1 h. The precipitate was collected, suspended in MeOH (30 mL) and the insolubles were removed by filtration. To the MeOH solution was added ether (20 mL) to precipitate the product. The white solid was collected and dried *in vacuo* to offer **118** (65 mg, 6%): mp 205-208 °C; 1H NMR (500 MHz, $CD_3OD+NaOD$) δ 8.17 (s, 1 H), 7.88 (d, 1 H), 7.80 (s, 1
20 H), 7.56-7.63 (m, 3 H), 7.35-7.41 (m, 3 H), 6.08 (bs, 1 H), 4.80 (bs, 2 H), 4.59-4.75 (m, 1 H), 3.72-3.82 (m, 1 H), 2.89-3.01 (m, 1 H), 1.90-1.99 (m, 4 H), 1.51 (d, 6 H), 1.29-1.40 (m, 2 H), 1.12-1.23 (m, 2 H); API MS m/z = 500 $[C_{28}H_{33}N_7O_2+H]^+$.

Example 102 - Preparation of Compound 119

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3-Thiopheneboronic acid (4.5 g, 35.2 mmol) and 6-chloronicotinamide (5.0 g, 32.0 mmol) were dissolved in DMA (150 mL), followed by the addition of 2N Na_2CO_3 (23 mL). N_2 gas was passed through the mixture for 1 h. $Pd(PPh_3)_4$ (0.74 g, 0.64 mmol) was added and the reaction mixture was heated to reflux for 24 h. The
30 reaction mixture was cooled to room temperature and poured into an ice-water (1 L) and stirred for 10 min. The precipitate was collected and washed with acetone. The collected solid was suspended in EtOAc (150 mL) and heated to reflux for 5 min. The solid was filtered and collected. After drying *in vacuo*, **119** (4.5 g, 69%) was

obtained: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.08 (s, 1 H), 8.34 (s, 1 H), 8.28 (d, 1 H), 8.20 (bs, 1 H), 7.99 (d, 1 H), 7.81 (d, 1 H), 7.71 (d, 1 H), 7.60 (bs, 1 H).

Example 103 - Preparation of Compound 120

5 To compound 119 (4.08 g, 20.0 mmol) suspended in THF (50 mL), was added 1M BH_3 -THF (164 mL). The mixture was heated to reflux for 9 h. The mixture was cooled with an ice-water bath and adjusted to a pH of 1-2, and stirred for 1 h at room temperature. The pH was adjusted to 9-10 (2N NaOH) and extracted with
10 EtOAc (3 x 50 mL). The combined organic phases were washed with H_2O (50 mL), brine (50 mL), and dried over Na_2SO_4 . After filtration and removal of the solvent, the residue was dissolved in EtOH (50 mL), followed by the addition of 1M HCl/ether (20 mL). The mixture was concentrated to dryness to provide **120** (2.03 g, 45%): ^1H NMR (500 MHz, CD_3OD) δ 8.93 (s, 1 H), 8.61 (d, 1 H), 8.51 (s, 1 H), 8.43 (d, 1 H),
15 7.81 (d, 1 H), 7.70 (d, 1 H), 3.30 (t, 2 H).

Example 104 - Preparation of Compound 121

Compound **120** (2 g, 8.82 mmol), 2,6-dichloropurine (1.5 g, 8.01
20 mmol), EtOH (50 mL), and (*i*-Pr) $_2\text{NEt}$ (3.8 mL, 22 mmol) were heated at reflux for 16 h. The reaction mixture was then cooled with an ice-water bath. The precipitate was collected and washed with EtOH, H_2O , and ether. The precipitate was dried *in vacuo* to obtain **121** (0.84 g, 31%): ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.02 (bs, 1 H), 8.76 (bs, 1 H), 8.63 (s, 1 H), 8.07 (bs, 2 H), 7.79 (bs, 2 H), 7.71 (d, 1 H), 7.64 (d, 1 H),
25 4.68 (bs, 2 H).

Example 105 - Preparation of Compound 122

Compound **121** (950 mg, 2.77 mmol) was dissolved in DMSO (50
30 mL), and then K_2CO_3 (2.07 g, 15.0 mmol) was added, followed by the addition of 2-iodopropane (830 μL , 8.31 mmol). The reaction mixture then was stirred at room temperature overnight. The reaction mixture was poured into an ice-water bath (400 mL), stirred for 10 min, and extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with H_2O (40 mL), brine (40 mL), and dried over

MgSO₄. After filtration and removal of the solvent, the residue was dissolved in hot EtOAc (40 mL), followed by the addition of hexanes (80 mL). The precipitate was collected and dried *in vacuo* to obtain **122** (798 mg, 90%): ¹H NMR (500 MHz, CDCl₃) δ 8.64 (s, 1 H), 7.83 (s, 1 H), 7.70-7.79 (m, 2 H), 7.60 (d, 1 H), 7.55 (d, 1 H), 7.36 (d, 1 H), 6.11 (bs, 1 H), 4.77-4.96 (m, 3 H), 1.53 (d, 6 H).

Example 106 - Preparation of Compound 123

Compound **122** (780.0 mg, 2.03 mmol), *trans*-1,4-diaminocyclohexane (2.3 g, 20.3 mmol), and EtOH (4 mL) were heated in a sealed tube to 150 °C for 20 h. The reaction mixture was poured into ice-water (150 mL) and stirred for 10 min. The resulting precipitate was washed with H₂O (2 x 20 mL) and dried. The solid was chromatographed on a silica gel column. After removal of the solvent and drying *in vacuo*, **123** (765 mg) was obtained: mp 78-81 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.63 (s, 1 H), 7.87 (s, 1 H), 7.72 (d, 1 H), 7.64 (d, 1 H), 7.55 (d, 1 H), 7.04-7.09 (m, 1 H), 6.92 (s, 1 H), 5.95 (bs, 1 H), 4.64 (bs, 2 H), 4.33-4.45 (m, 2 H), 3.74-3.77 (m, 1 H), 2.67-2.76 (m, 1 H), 2.13 (d, 2 H), 1.90 (d, 2 H), 1.63 (bs, 2 H), 1.54 (d, 6 H), 1.19-1.30 (m, 4 H); ¹³C NMR (CDCl₃) δ 159.1, 155.0, 152.7, 151.3, 149.3, 143.3, 142.3, 136.2, 134.8, 133.4, 126.4, 126.4, 123.5, 120.2, 114.8, 50.4, 50.3, 46.5, 42.0, 35.7, 32.3, 22.8; API MS *m/z* = 463 [C₂₄H₃₀N₈S+H]⁺.

Example 107 - Preparation of Compound 124

To an ice-cold solution of compound **123** (420 mg, 0.91 mmol) in CH₂Cl₂ (20 mL) was added pyridine (110 μL, 1.4 mmol), DMAP (11.0 mg, 0.09 mmol) and Ac₂O (94.2 μL, 1 mmol). The reaction mixture was stirred for 30 min at 0 °C, followed by 2 h at room temperature. After removal of the solvent, the residue was chromatographed on a silica gel column. The resulting solid was recrystallized with EtOAc/MeOH and dried *in vacuo* to give **124** (350 mg, 79%): mp 249-252 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.61 (s, 1 H), 7.85 (s, 1 H), 7.70 (d, 1 H), 7.62 (d, 1 H), 7.53 (d, 1 H), 7.48 (s, 1 H), 7.38 (d, 1 H), 6.00 (bs, 1 H), 5.25 (d, 1 H), 4.77 (bs, 2 H), 4.53-4.72 (m, 2 H), 3.68-3.77 (m, 2 H), 2.10 (d, 2 H), 2.00 (d, 2 H), 1.94 (s, 3 H), 1.52 (d, 6 H), 1.17-1.28 (m, 4 H); ¹³C NMR (CDCl₃) δ 169.4, 159.0, 155.0, 152.8, 149.2.

142.8, 142.3, 136.1, 134.9, 133.4, 126.5, 126.4, 123.5, 120.2, 114.9, 50.1, 48.3, 46.5, 42.2, 32.2, 32.1, 22.8: API MS $m/z = 505$ $[\text{C}_{26}\text{H}_{32}\text{N}_8\text{OS}+\text{H}]^+$.

Example 108 - Description of Biological Assays

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A. Immunopurification of CyclinA/cdk2 and CyclinE/cdk2 Complexes.

CyclinA/cdk2 and cyclinE/cdk2 assays were carried out with cyclin/cdk complexes isolated from HeLa S-3 suspension cultures. HeLa cells were grown in spinner flasks at 37 °C in Joklik's modified minimum essential media (MEM) supplemented with 7% horse serum. After growing in medium supplemented with 2 mM thymidine for 16-18 h, cultures were arrested at the G1/S border and cyclinA/cdk2 and cyclinE/cdk2 were isolated from cell lysates by immunoprecipitation with antibodies specifically directed against each cyclin subunit. Rabbit anti-cyclinA (H-432) and the mouse monoclonal antibody against cyclinE (HE111) were purchased from Santa Cruz Biotechnology. Cells blocked at the appropriate stage of the cell cycle were disrupted in lysis buffer (50 mM Tris, pH 8.0, 250 mM NaCl, 0.5% NP-40 plus protease and phosphatase inhibitors) and centrifuged at 10,000 x g to remove insoluble material. To isolate cyclin/cdk complexes, 1 µg of anti-cyclin antibody was incubated with lysate from 1×10^7 cells for 1 h at 4 °C. Protein A-coated agarose beads were then added for 1 h to collect antibody-bound immune complexes. The immobilized cyclin/cdk complexes were then washed 4 x with lysis buffer to reduce nonspecific protein binding. The complexes were then washed 1 x in kinase assay buffer (50 mM Tris-HCl, pH 7.4, 10 mM MgCl_2 , 1 mM DTT) and aliquoted into individual assay tubes.

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B. Immunopurification of CyclinB/cdk1 Complex.

HeLa cells are blocked at the G1/S border by culturing in the presence of 2 mM thymidine for 20 h. The cells are then rinsed 3x in phosphate buffered saline and resuspended in regular medium. After 4 h of culture, the mitotic blocker, nocodazole is added to a final concentration of 75 ng/ml. Sixteen hours later, the cells are harvested by centrifugation, washed in PBS, and lysed in cold Lysis Buffer (50 mM Tris pH 8.0, 250 mM NaCl, 0.5% NP-40, 1 mM DTT, 25 µg/ml leupeptin, 25 µg/ml aprotinin, 15 µg/ml benzamidin, 1 mM PMSF, 50 mM sodium fluoride, 1 mM

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sodium orthovanadate) for 15 min at 1×10^7 cells/ml. The lysate is then clarified by centrifugation at $10,000 \times g$ for 10 min. The supernatant is collected and diluted 1:5 with Lysis Buffer. Monoclonal antibody against cyclinB (GNS1) is added to the supernatant to a final concentration of 5 $\mu\text{g/ml}$ and shaken at 4 °C for 2 h. The immune complexes are then collected by the addition of 200 μl of protein agarose beads for 1 h. The beads are washed 4x in lysis buffer and 1x in kinase assay buffer.

C. Protein Kinase Assays and Determination of IC_{50} Values.

CyclinA/cdk2 assays were carried out with complexes isolated from 0.5×10^6 cells. CyclinE/cdk2 assays were carried out with complexes isolated from 4×10^6 cells. CyclinB/cdk1 assays were carried out with complexes isolated from 4×10^4 cells. After centrifugation, the wash buffer was removed and the complexes resuspended in 15 μl of kinase assay buffer (kinase wash buffer + 167 $\mu\text{g/ml}$ histone H1). Compounds being tested for inhibition were added prior to the addition of [γ ^{32}P] ATP to a final concentration of 15 μM . The tubes were incubated at 30 °C for 5 min and the reactions were stopped by the addition of an equal volume of 2 x SDS-PAGE sample buffer. The samples were then subjected to electrophoresis on 10% SDS-PAGE to resolve the histone H1 from other reaction components. The amount of radioactive phosphate transferred to histone H1 was quantified on a Storm Phosphorimager (Molecular Dynamics).

Prior to the protein kinase assay, test compounds were dissolved in DMSO at a concentration of 25 mM and were diluted to produce final concentrations of 0.1, 1.0, and 10.0 μM in the kinase assays. To eliminate possible effects of differences in DMSO concentration, the DMSO was kept constant at 0.04%, including the control reaction. Duplicate assays were performed at each concentration. The activity was plotted as the percent of activity in the absence of added test compound versus test compound concentration. IC_{50} values were calculated using GraphPad Prism data analysis software.

D. Measuring the Inhibition of Cell Growth.

Growth inhibition (GI_{50}) values were measured with HeLa S-3 cells selected for growth on plastic. The procedure was based on the protocol of Skehan *et al.* (Skehan, P., *et al.*, J. Natl. Cancer Inst., 82:1107-1112 (1990), which is hereby incorporated by reference) HeLa cells were plated at 2×10^4 cells/well in 96 well

plates. One day later, a control plate was fixed by addition of TCA to 5%. After five rinses with tap water the plate was air dried and stored at 4 °C. Test compounds were added to the remaining plates at 10-fold dilutions between 0.01 and 100 µM. Two days later all plates were fixed as described above. Cells were then stained by the addition of 100 µl per well of 0.4% sulforhodamine B (SRB) in 1% acetic acid for 30 min at 4 °C. Wells were then quickly rinsed 5 x with acetic acid (1%) and allowed to air dry. The SRB was then solubilized by the addition of 100 µl per well of unbuffered 10 mM Tris base. Dye was quantified by measuring absorbance at 490 nm on a Molecular Devices kinetic microplate reader. Growth at each inhibitor concentration relative to the untreated control was calculated according to the following equation: percent growth = $100 \times (T - T_0) / (C - T_0)$, where T was the average optical density (OD) of the test wells after 2 days of treatment. T₀ was the average OD of the wells in the control plate on day 0 and C was the average OD of untreated wells. Plots of percent growth versus inhibitor concentration were used to determine the GI₅₀.

The data below shown in Table 2 summarizes the *in vitro* cyclin/cdk inhibition constants (IC₅₀) and growth inhibition constants (GI₅₀) of HeLa Cells for the compounds of the current invention. Replicate experimental results are summarized below.

Table 2: In Vitro Cyclin/cdk Inhibition (IC₅₀) and Growth Inhibition (GI₅₀) of HeLa Cells

For Compounds of the Current Invention.

| Compound | IC ₅₀ CyclinA/cdk2 (μ M) | IC ₅₀ CyclinE/cdk2 (μ M) | IC ₅₀ CyclinB/cdk1 (μ M) | GI ₅₀ HeLa Cells (μ M) |
|----------|---------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------|
| 5 | > 10 | 12 | 7 | 5 |
| | 0.4 | 0.6 | | > 10 |
| 12 | 2 | 1 | 3 | 0.06 |
| | 0.7 | 3 | | 0.003 |
| | 0.9 | 0.5 | | 0.001 |
| | 0.2 | 0.1 | | 0.02 |
| 13 | | | | 0.0001 |
| | 4 | 2 | 4 | 3 |
| | 1 | 0.3 | | 2 |
| 14 | 0.8 | 0.9 | | |
| | 3 | 0.4 | 7 | 0.4 |
| 17 | 3 | 2 | | 0.03 |
| | 3 | | | 0.03 |
| 17 | 1 | 1 | 10 | 0.4 |
| | 2 | 0.9 | 3 | 0.6 |
| | 1 | 0.2 | 11 | 0.25 |
| | > 10 | 9 | | 0.4 |
| | 10 | 2 | | 0.3 |
| | | | | 0.4 |
| 25 | 1 | 4 | > 10 | 2 |
| | 6 | 1 | > 10 | 0.4 |
| | > 10 | 9 | | > 1 |
| 32 | 2 | 3 | -- | 5 |
| | 5 | 0.9 | | 0.7 |
| 33 | > 10 | 4 | > 10 | 1 |
| | 13 | 6 | | 2 |
| | 8 | | | 0.9 |
| 34 | 12 | 5 | > 10 | 7 |
| | 13 | 2 | | 6 |
| 36 | | | | 7 |
| | > 10 | > 10 | > 10 | 20 |
| | > 10 | > 10 | | 20 |
| 38 | > 10 | | | > 10 |
| | > 10 | > 10 | > 10 | 0.6 |
| | | > 10 | | 1 |
| 40 | | | | 0.6 |
| | > 10 | > 10 | > 10 | 9 |
| | > 10 | > 10 | | 25 |
| 43 | | | | > 10 |
| | > 10 | > 10 | > 10 | 4 |
| | > 10 | > 10 | | 4 |
| 46 | | | | 8 |
| | > 10 | 6 | > 10 | 25 |
| | 8 | 3 | | > 10 |

| | | | | |
|----|----------------------------|---------------------------|------------|-------------------------------------|
| 48 | 22 6 | 1 5 | > 10 | 0.3 0.6 0.5 |
| 50 | > 10 7 | > 10 9 | > 10 | 3 > 10 |
| 53 | > 10 > 10 | 15 4 | > 10 | 0.2 0.3 0.5 |
| 58 | 11 4 | 2 4 | 12 | 2 0.5 0.7 |
| 60 | > 10 0.4 | 12 > 10 | > 10 | 7 6 |
| 73 | > 50 14 > 10 > 10 | 4 12 > 10 > 10 | > 10 | 0.3 0.5 0.3 0.5 |
| 74 | 5 2 1 | 2 3 2 | 6 | 0.2 0.01 0.05 0.03 0.05 |
| 75 | 3 | 3 | 6 | 0.09 0.02 0.005 |
| 76 | 12 11 3 | 3 5 2 | 6 | 0.07 0.01 0.06 0.2 0.04 |
| 77 | > 10 > 10 | 4 14 | > 10 | 0.15 0.5 0.3 |
| 78 | 0.9 0.9 0.7 | 0.6 0.3 0.2 | 0.8 0.8 | 0.05 0.025 0.08 0.002 |
| 79 | 10 0.5 1 | 2 0.1 0.08 | 3 | 0.07 0.007 0.004 0.4 |
| 80 | > 10 > 10 | > 10 4 2 | > 10 | > 100 > 10 |
| 86 | 0.9 0.7 0.4 0.6 | 0.4 0.2 0.4 0.03 | 2 | 0.2 0.03 0.01 0.01 0.2 |

- 118 -

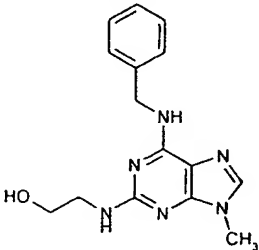
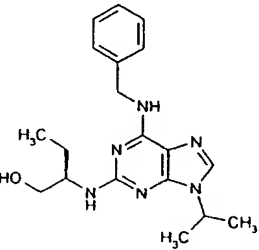
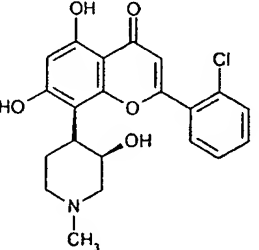
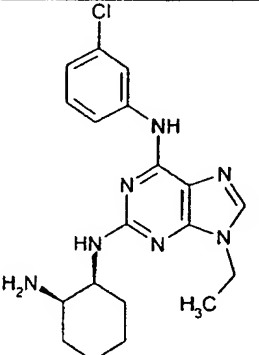
| | | | | |
|-----|----------------|-----------------|------|--------------------------------------------------------------------|
| 87 | 4 2 0.5 | 1 0.3 0.1 | 5 | 0.07 0.01 0.004 0.006 0.03 0.006 0.001 0.0001 |
| 88 | 3 > 10 2 | 4 > 10 5 | > 10 | 0.1 0.05 0.04 0.005 |
| 93 | 0.2 0.3 | 0.09 0.1 | 0.9 | 0.3 0.08 0.3 |
| 94 | 0.6 0.2 | 0.3 0.3 | 0.4 | 0.1 0.07 0.4 |
| 95 | 1 2 | 1 0.7 | 4 | 0.08 0.003 0.0005 |
| 96 | 8 | 4 | 6 | 0.04 0.01 |
| 97 | > 10 | 3 | 10 | 3 |
| 98 | 6 2 | 2 2 | > 10 | > 10 11 |
| 99 | > 10 | 9 | > 10 | 5 |
| 100 | > 10 | 4 | > 10 | 0.6 |
| 101 | 3 0.9 | 1 0.7 | 4 | 1 1 |
| 102 | > 10 | 4 | -- | 4 |
| 103 | 0.6 0.7 | 0.2 0.2 | 1 | 0.03 0.008 0.02 0.01 |
| 104 | 7 8 | 1 1 | 2 | 0.4 0.2 |
| 106 | 11 4 | 3 1 | -- | 0.3 0.1 |
| 107 | 1 4 | 2 | -- | 0.4 0.3 |
| 108 | 10 > 10 | > 10 > 10 | -- | 3 5 |
| 109 | 0.6 | 0.1 | -- | 0.04 < 0.0001 |
| 110 | 0.6 | 2 | -- | 0.02 0.03 0.02 0.01 |
| 111 | 0.2 | 0.07 | -- | 0.02 0.0006 |

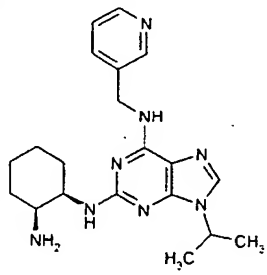
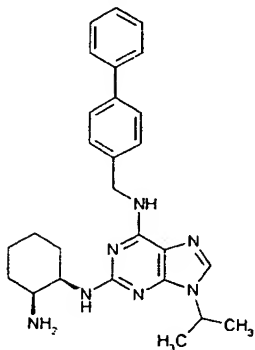
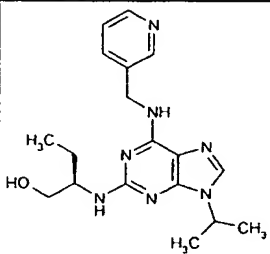
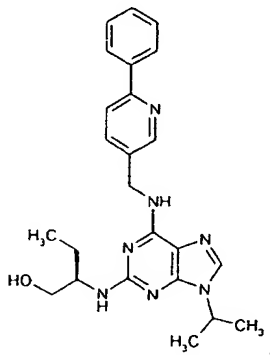
| | | | | |
|-----|------|------|----|---------------------------------------------|
| 112 | 2 | 2 | -- | < 0.001 0.002 0.02 0.006 0.0006 |
| 113 | 0.4 | 0.3 | -- | < 0.001 0.00001 0.03 0.001 0.02 |
| 114 | 3 | 0.7 | -- | > 10 |
| 115 | 3 | 0.4 | -- | 3 |
| 116 | > 10 | > 10 | -- | > 10 > 10 |
| 117 | > 10 | 3 | -- | 3 |
| 118 | 6 | 1 | -- | > 10 > 10 |
| 123 | 0.2 | 0.04 | -- | < 0.001 < 0.001 0.0001 |
| 124 | 2 | 0.8 | -- | 0.003 < 0.001 < 0.0001 |

The data below shown in Table 3 summarizes the in vitro cyclin/cdk inhibition (IC_{50}) and growth inhibition (GI_{50}) of HeLa Cells for several reference compounds in comparison to several compounds of the current invention. The chemical structures are provided.

Table 3: In Vitro cyclin/cdk Inhibition (IC₅₀) and Growth Inhibition (GI₅₀) of HeLa Cells
For Reference Compounds in Comparison to Several Compounds of the Current Invention.

5

| Compound | Structure | IC ₅₀ CyclinA/cdk2 (μ M) | IC ₅₀ CyclinE/cdk2 (μ M) | IC ₅₀ CyclinB/cdk1 (μ M) | GI ₅₀ HeLa Cells (μ M) |
|--------------|-------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|----------------------------------------------|
| Olomoucine |  | 0.5-24 (n > 10) | 1-14 (n > 10) | 7-23 (n > 10) | 75 |
| Roscovitine |  | 2.1 4 3 | 0.04 0.7 | -- | 30 25 30 > 10 25 |
| Flavopiridol |  | 0.06 0.2 | 0.6 0.04 | 0.06 (n = 2) | 0.18 |
| 125 |  | 1 | 0.1 | 0.6 | 3 |

| | | | | | |
|-----|-------------------------------------------------------------------------------------|-------------------|-----------------------|-------------------|---------------------|
| 126 |  | 0.6 0.8 | 0.06 0.06 | 2 0.2 | 2 4 6 |
| 74 |  | 5 | 2 | 6 | 0.2 0.01 0.05 |
| 127 |  | 0.3-2 (n > 15) | 0.04-0.07 (n > 15) | 0.5-2 (n > 15) | 7-15 (n > 5) |
| 88 |  | 3 | 4 | > 10 | 0.1 0.05 0.04 |

The following data in Tables 4, 5, 6, and 7 summarize the growth inhibition properties of several compounds of the current invention and olomoucine against 60-human transformed cell lines. These data were cooperatively obtained at the National Cancer Institute in their 60-cell line growth inhibition assay according to published procedures (Boyd, M.R.,

"Anticancer Drug Development Guide." Preclinical Screening, Clinical Trials, and Approval:

Teicher, B. Ed.: Humana Press: Totowa, NJ, 23-42 (1997), which is hereby incorporated by reference).

Table 4: In Vitro Growth Inhibition (GI_{50}) of NCI Human Transformed Cell Lines of Several Compounds of the Current Invention.

| Cancer Type | Cell Line | 73 GI_{50} (μ M) | 17 GI_{50} (μ M) | 33 GI_{50} (μ M) | 38 GI_{50} (μ M) |
|---------------------|-----------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Breast | BT-549 | 0.25 | 0.40 | 51.3 | 0.32 |
| Breast | HS 578T | 0.10 | 6.31 | -- | -- |
| Breast | MCF7 | 0.16 | 0.16 | 5.2 | 0.20 |
| Breast | MDA-MB-231/ATCC | 0.50 | -- | -- | 0.06 |
| Breast | MDA-MB-435 | 0.25 | 0.20 | 4.9 | 0.05 |
| Breast | MDA-N | 0.13 | 0.11 | -- | -- |
| Breast | NCI/ADR-RES | 0.40 | 0.28 | 6.3 | 0.32 |
| Breast | T-47D | 0.25 | 0.13 | 3.9 | 0.25 |
| CNS | SF-268 | 0.16 | 0.04 | 6.3 | 0.20 |
| CNS | SF-295 | 0.25 | 0.19 | 7.8 | 0.50 |
| CNS | SF-539 | 0.76 | 0.40 | 89.1 | 1.26 |
| CNS | SNB-19 | 0.43 | 0.14 | 38.0 | 0.50 |
| CNS | SNB-75 | 0.02 | 0.02 | -- | -- |
| CNS | U251 | 0.32 | 0.40 | 3.7 | 0.20 |
| Colon | COLO 205 | 0.28 | 0.05 | 7.8 | 0.16 |
| Colon | HCC-2998 | 0.20 | 0.03 | > 1000 | 7.94 |
| Colon | HCT-116 | 0.20 | 0.16 | 6.2 | 0.32 |
| Colon | HCT-15 | 0.18 | 0.04 | 8.9 | 0.25 |
| Colon | HT29 | -- | 0.10 | 8.9 | 0.25 |
| Colon | KM12 | 0.13 | 0.03 | 4.1 | 0.16 |
| Colon | SW-620 | -- | 0.01 | 2.9 | 0.03 |
| Leukemia | CCRF-CEM | 0.25 | 0.16 | 4.6 | 0.20 |
| Leukemia | HL-60(TB) | -- | -- | 3.2 | 0.04 |
| Leukemia | K-562 | 0.16 | 0.16 | 3.1 | 0.25 |
| Leukemia | MOLT-4 | 0.32 | 0.25 | 3.8 | 0.25 |
| Leukemia | RPMI-8226 | 0.03 | 0.03 | 1.5 | -- |
| Leukemia | SR | -- | 0.50 | 4.5 | 3.98 |
| Melanoma | LOX IMVI | -- | 0.32 | 16.6 | 0.40 |
| Melanoma | M14 | 0.03 | 0.03 | 7.8 | 0.05 |
| Melanoma | MALME-3M | 0.27 | 19.95 | 11.7 | 0.25 |
| Melanoma | SK-MEL-2 | 0.63 | 1.00 | > 1000 | 2.00 |
| Melanoma | SK-MEL-28 | 0.45 | 0.12 | 5.9 | 0.03 |
| Melanoma | SK-MEL-5 | 0.25 | 0.32 | 16.2 | 0.32 |
| Melanoma | UACC-257 | 0.16 | 0.20 | 75.9 | 0.50 |
| Melanoma | UACC-62 | 0.30 | 0.27 | 8.3 | 1.00 |
| Non-Small Cell Lung | A549/ATCC | 0.03 | 0.03 | 4.6 | 0.13 |
| Non-Small Cell Lung | EKVX | 0.25 | 2.51 | 6.9 | 0.20 |
| Non-Small Cell Lung | HOP-62 | 0.06 | 0.20 | > 1000 | 0.32 |

| | | | | | |
|---------------------|-----------|------|--------|--------|------|
| Non-Small Cell Lung | HOP-92 | 1.00 | 1.58 | -- | 0.32 |
| Non-Small Cell Lung | NCI-H226 | 0.22 | 0.11 | -- | -- |
| Non-Small Cell Lung | NCI-H23 | 0.32 | 0.16 | 26.3 | 0.32 |
| Non-Small Cell Lung | NCI-H322M | 0.16 | > 1000 | 38.9 | 0.40 |
| Non-Small Cell Lung | NCI-H460 | 0.40 | 0.41 | 25.7 | 3.16 |
| Non-Small Cell Lung | NCI-H522 | -- | -- | 4.2 | -- |
| Ovarian | IGROV1 | 0.32 | 0.20 | 10.0 | 0.16 |
| Ovarian | OVCAR-3 | 0.30 | 0.65 | > 1000 | 1.00 |
| Ovarian | OVCAR-4 | 0.32 | 0.32 | 31.6 | 1.26 |
| Ovarian | OVCAR-5 | 0.25 | 0.26 | > 1000 | 0.40 |
| Ovarian | OVCAR-8 | -- | 0.13 | 6.6 | 0.25 |
| Ovarian | SK-OV-3 | 0.95 | 0.40 | > 1000 | 3.98 |
| Prostate | DU-145 | 7.08 | 0.63 | 17.8 | 1.26 |
| Prostate | PC-3 | 0.35 | 0.20 | > 1000 | 0.40 |
| Renal | 786-0 | 0.20 | 0.25 | 18.6 | 0.32 |
| Renal | A498 | 2.88 | 1.58 | -- | 1.26 |
| Renal | ACHN | 0.32 | 0.40 | 5.2 | 2.00 |
| Renal | CAKI-1 | 1.66 | 0.13 | 4.4 | 0.20 |
| Renal | RXF 393 | 0.09 | 0.02 | 13.2 | 0.13 |
| Renal | SN12C | -- | 0.56 | -- | -- |
| Renal | TK-10 | -- | -- | 8.3 | 0.40 |
| Renal | UO-31 | 0.06 | 0.10 | 8.1 | 0.13 |

Table 5: In Vitro Growth Inhibition (GI_{50}) of NCI Human Transformed Cell Lines of Several Compounds of the Current Invention.

5

| Cancer Type | Cell Line | 43 GI_{50} (μ M) | 48 GI_{50} (μ M) | 75 GI_{50} (μ M) | 76 GI_{50} (μ M) |
|-------------|-----------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Breast | BT-549 | 4.0 | 0.01 | < 0.01 | < 0.01 |
| Breast | HS 578T | -- | 0.03 | < 0.01 | < 0.01 |
| Breast | MCF7 | 2.7 | 0.25 | < 0.01 | < 0.01 |
| Breast | MDA-MB-231/ATCC | 3.2 | 0.09 | < 0.01 | < 0.01 |
| Breast | MDA-MB-435 | 2.1 | -- | -- | -- |
| Breast | MDA-N | -- | 0.02 | < 0.01 | < 0.01 |
| Breast | NCI/ADR-RES | 5.2 | 0.12 | 0.48 | 0.015 |
| Breast | T-47D | 2.2 | 0.15 | < 0.01 | < 0.01 |
| CNS | SF-268 | 3.0 | < 0.01 | < 0.01 | < 0.01 |
| CNS | SF-295 | 4.0 | 0.24 | < 0.01 | < 0.01 |
| CNS | SF-539 | 3.4 | 0.38 | 0.02 | 0.054 |
| CNS | SNB-19 | 5.0 | 0.02 | < 0.01 | < 0.01 |
| CNS | SNB-75 | -- | < 0.01 | < 0.01 | < 0.01 |
| CNS | U251 | 2.3 | 0.17 | < 0.01 | 0.020 |
| Colon | COLO 205 | 1.6 | 0.03 | < 0.01 | < 0.01 |
| Colon | HCC-2998 | 3.4 | -- | -- | -- |
| Colon | HCT-116 | 2.1 | 0.19 | < 0.01 | 0.014 |

| | | | | | |
|---------------------|-----------|------|--------|--------|--------|
| Colon | HCT-15 | 3.9 | 0.02 | 0.03 | < 0.01 |
| Colon | HT29 | 3.6 | < 0.01 | < 0.01 | < 0.01 |
| Colon | KM12 | 2.3 | 0.02 | < 0.01 | < 0.01 |
| Colon | SW-620 | 1.6 | < 0.01 | < 0.01 | < 0.01 |
| Leukemia | CCRF-CEM | 2.8 | 0.03 | < 0.01 | < 0.01 |
| Leukemia | HL-60(TB) | 2.1 | -- | -- | -- |
| Leukemia | K-562 | 3.1 | 0.16 | < 0.01 | < 0.01 |
| Leukemia | MOLT-4 | 2.0 | 0.05 | < 0.01 | < 0.01 |
| Leukemia | RPMI-8226 | -- | < 0.01 | < 0.01 | < 0.01 |
| Leukemia | SR | 2.2 | 0.16 | < 0.01 | < 0.01 |
| Melanoma | LOX IMVI | 3.4 | 0.19 | < 0.01 | < 0.01 |
| Melanoma | M14 | 2.2 | < 0.01 | < 0.01 | < 0.01 |
| Melanoma | MALME-3M | 3.0 | 0.13 | < 0.01 | < 0.01 |
| Melanoma | SK-MEL-2 | 61.7 | 0.48 | 0.02 | 0.112 |
| Melanoma | SK-MEL-28 | 2.3 | < 0.01 | < 0.01 | < 0.01 |
| Melanoma | SK-MEL-5 | 2.1 | 0.17 | 0.01 | 0.013 |
| Melanoma | UACC-257 | 4.8 | 0.04 | < 0.01 | < 0.01 |
| Melanoma | UACC-62 | 3.3 | 0.10 | 0.01 | 0.018 |
| Non-Small Cell Lung | A549/ATCC | 4.1 | < 0.01 | < 0.01 | < 0.01 |
| Non-Small Cell Lung | EKVX | 2.8 | -- | -- | -- |
| Non-Small Cell Lung | HOP-62 | 3.3 | 0.03 | < 0.01 | < 0.01 |
| Non-Small Cell Lung | HOP-92 | 2.6 | 0.46 | < 0.01 | 0.017 |
| Non-Small Cell Lung | NCI-H226 | -- | -- | -- | -- |
| Non-Small Cell Lung | NCI-H23 | 4.3 | 0.07 | < 0.01 | < 0.01 |
| Non-Small Cell Lung | NCI-H322M | 3.5 | 0.03 | < 0.01 | < 0.01 |
| Non-Small Cell Lung | NCI-H460 | 3.2 | 0.25 | < 0.01 | 0.047 |
| Non-Small Cell Lung | NCI-H522 | -- | < 0.01 | < 0.01 | < 0.01 |
| Ovarian | IGROV1 | 3.4 | 0.23 | < 0.01 | < 0.01 |
| Ovarian | OVCAR-3 | 9.3 | 0.17 | < 0.01 | < 0.01 |
| Ovarian | OVCAR-4 | 8.9 | 0.20 | < 0.01 | < 0.01 |
| Ovarian | OVCAR-5 | 3.6 | 0.16 | < 0.01 | < 0.01 |
| Ovarian | OVCAR-8 | 3.9 | 0.10 | < 0.01 | < 0.01 |
| Ovarian | SK-OV-3 | 72.4 | 1.38 | 0.03 | 0.051 |
| Prostate | DU-145 | 2.6 | 0.55 | < 0.01 | 0.043 |
| Prostate | PC-3 | 38.9 | 0.23 | < 0.01 | < 0.01 |
| Renal | 786-0 | 3.1 | 0.25 | < 0.01 | < 0.01 |
| Renal | A498 | 3.0 | 0.39 | 0.01 | < 0.01 |
| Renal | ACHN | 3.1 | 0.25 | 0.02 | 0.025 |
| Renal | CAKI-1 | 3.0 | -- | -- | -- |
| Renal | RXF 393 | 1.9 | < 0.01 | < 0.01 | < 0.01 |
| Renal | SN12C | -- | 0.03 | < 0.01 | < 0.01 |
| Renal | TK-10 | 3.2 | 0.37 | < 0.01 | 0.013 |
| Renal | UO-31 | 2.8 | < 0.01 | 0.03 | < 0.01 |

Table 6: In Vitro Growth Inhibition (GI₅₀) of NCI Human Transformed Cell Lines of Several Compounds of the Current Invention.

| Cancer Type | Cell Line | 79 GI ₅₀ (μM) | 87 GI ₅₀ (μM) | 12 GI ₅₀ (μM) |
|---------------------|-----------------|--------------------------|--------------------------|--------------------------|
| Breast | BT-549 | < 0.01 | 0.02 | 0.041 |
| Breast | HS 578T | < 0.01 | < 0.01 | < 0.005 |
| Breast | MCF7 | < 0.01 | 0.04 | < 0.005 |
| Breast | MDA-MB-231/ATCC | < 0.01 | < 0.01 | < 0.005 |
| Breast | MDA-MB-435 | < 0.01 | < 0.01 | < 0.005 |
| Breast | MDA-N | < 0.01 | 0.014 | < 0.005 |
| Breast | NCI/ADR-RES | 0.86 | 0.28 | 1.26 |
| Breast | T-47D | < 0.01 | 0.048 | 0.0088 |
| CNS | SF-268 | < 0.01 | < 0.01 | < 0.005 |
| CNS | SF-295 | < 0.01 | 0.047 | 0.018 |
| CNS | SF-539 | < 0.01 | 0.081 | 0.022 |
| CNS | SNB-19 | < 0.01 | 0.038 | 0.016 |
| CNS | SNB-75 | < 0.01 | 0.012 | < 0.005 |
| CNS | U251 | < 0.01 | 0.028 | 0.0078 |
| Colon | COLO 205 | < 0.01 | < 0.01 | < 0.005 |
| Colon | HCC-2998 | < 0.01 | < 0.01 | < 0.005 |
| Colon | HCT-116 | < 0.01 | 0.037 | 0.0089 |
| Colon | HCT-15 | < 0.01 | 0.066 | 0.17 |
| Colon | HT29 | < 0.01 | < 0.01 | < 0.005 |
| Colon | KM12 | < 0.01 | < 0.01 | < 0.005 |
| Colon | SW-620 | < 0.01 | < 0.01 | < 0.005 |
| Leukemia | CCRF-CEM | < 0.01 | < 0.01 | < 0.005 |
| Leukemia | HL-60(TB) | < 0.01 | < 0.01 | < 0.005 |
| Leukemia | K-562 | < 0.01 | 0.024 | < 0.005 |
| Leukemia | MOLT-4 | < 0.01 | 0.02 | < 0.005 |
| Leukemia | RPMI-8226 | < 0.01 | < 0.01 | < 0.005 |
| Leukemia | SR | < 0.01 | 0.032 | < 0.005 |
| Melanoma | LOX IMVI | < 0.01 | 0.027 | < 0.005 |
| Melanoma | M14 | < 0.01 | < 0.01 | < 0.005 |
| Melanoma | MALME-3M | < 0.01 | 0.024 | 0.010 |
| Melanoma | SK-MEL-2 | < 0.01 | 0.056 | 0.0096 |
| Melanoma | SK-MEL-28 | < 0.01 | < 0.01 | 0.01 |
| Melanoma | SK-MEL-5 | < 0.01 | 0.028 | 0.014 |
| Melanoma | UACC-257 | < 0.01 | 0.017 | 0.008 |
| Melanoma | UACC-62 | < 0.01 | 0.045 | 0.027 |
| Non-Small Cell Lung | A549/ATCC | < 0.01 | < 0.01 | < 0.005 |
| Non-Small Cell Lung | EKVX | < 0.01 | 0.081 | 0.023 |
| Non-Small Cell Lung | HOP-62 | < 0.01 | 0.01 | < 0.005 |
| Non-Small Cell Lung | HOP-92 | < 0.01 | 0.088 | 0.011 |
| Non-Small Cell Lung | NCI-H226 | < 0.01 | 0.0052 | 0.021 |
| Non-Small Cell Lung | NCI-H23 | < 0.01 | 0.022 | < 0.005 |
| Non-Small Cell Lung | NCI-H322M | < 0.01 | 0.021 | < 0.005 |
| Non-Small Cell Lung | NCI-H460 | < 0.01 | 0.22 | 0.015 |
| Non-Small Cell Lung | NCI-H522 | < 0.01 | < 0.01 | < 0.005 |
| Ovarian | IGROVI | < 0.01 | 0.052 | 0.013 |

| | | | | |
|----------|---------|--------|--------|---------|
| Ovarian | OVCAR-3 | < 0.01 | 0.05 | 0.012 |
| Ovarian | OVCAR-4 | < 0.01 | 0.048 | < 0.005 |
| Ovarian | OVCAR-5 | < 0.01 | 0.051 | 0.017 |
| Ovarian | OVCAR-8 | < 0.01 | 0.033 | 0.0076 |
| Ovarian | SK-OV-3 | < 0.01 | 0.35 | 0.018 |
| Prostate | DU-145 | < 0.01 | 0.22 | 0.017 |
| Prostate | PC-3 | < 0.01 | 0.018 | < 0.005 |
| Renal | 786-0 | < 0.01 | 0.047 | 0.0065 |
| Renal | A498 | < 0.01 | 0.10 | 0.016 |
| Renal | ACHN | < 0.01 | 0.19 | 0.039 |
| Renal | CAKI-1 | < 0.01 | 0.064 | 0.038 |
| Renal | RXF 393 | < 0.01 | 0.011 | < 0.005 |
| Renal | SN12C | < 0.01 | < 0.01 | < 0.005 |
| Renal | TK-10 | < 0.01 | 0.029 | 0.01 |
| Renal | UO-31 | < 0.01 | 0.016 | 0.063 |

Table 7: In Vitro Growth Inhibition (GI₅₀) of NCI Human Transformed Cell Lines of Several Compounds of the Current Invention and Olomoucine.

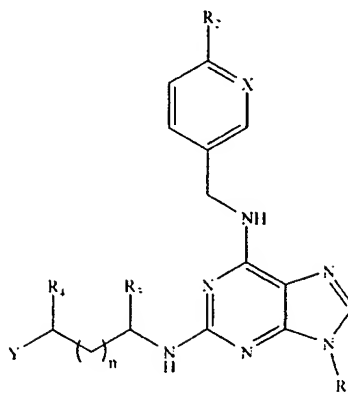
| Cancer Type | Cell Line | 74 GI ₅₀ (μM) | 78 GI ₅₀ (μM) | 77 GI ₅₀ (μM) | Olomoucine GI ₅₀ (μM) |
|-------------|-----------------|--------------------------|--------------------------|--------------------------|----------------------------------|
| Breast | BT-549 | 0.16 | 0.04 | < 0.01 | 79 |
| Breast | HS 578T | < 0.01 | -- | < 0.01 | 63 |
| Breast | MCF7 | < 0.01 | < 0.01 | 0.03 | 50 |
| Breast | MDA-MB-231/ATCC | < 0.01 | < 0.01 | 0.04 | 100 |
| Breast | MDA-MB-435 | -- | -- | -- | 63 |
| Breast | MDA-N | < 0.01 | < 0.01 | 0.01 | 79 |
| Breast | NCI/ADR-RES | 0.24 | 14.45 | 0.03 | 100 |
| Breast | T-47D | < 0.01 | 0.03 | 0.01 | 63 |
| CNS | SF-268 | < 0.01 | -- | < 0.01 | 50 |
| CNS | SF-295 | < 0.01 | 0.21 | 0.04 | 79 |
| CNS | SF-539 | 0.07 | -- | 0.22 | 32 |
| CNS | SNB-19 | < 0.01 | < 0.01 | 0.03 | 63 |
| CNS | SNB-75 | < 0.01 | < 0.01 | < 0.01 | 25 |
| CNS | U251 | < 0.01 | 0.02 | 0.09 | 50 |
| Colon | COLO 205 | < 0.01 | < 0.01 | 0.02 | 32 |
| Colon | HCC-2998 | -- | < 0.01 | -- | 63 |
| Colon | HCT-116 | < 0.01 | 0.03 | 0.05 | 40 |
| Colon | HCT-15 | < 0.01 | 1.48 | < 0.01 | 40 |
| Colon | HT29 | < 0.01 | < 0.01 | < 0.01 | 63 |
| Colon | KM12 | < 0.01 | < 0.01 | < 0.01 | 40 |
| Colon | SW-620 | < 0.01 | < 0.01 | < 0.01 | 40 |
| Leukemia | CCRF-CEM | < 0.01 | -- | < 0.01 | 40 |
| Leukemia | HL-60(TB) | -- | < 0.01 | -- | 40 |
| Leukemia | K-562 | < 0.01 | 0.02 | 0.02 | 100 |
| Leukemia | MOLT-4 | < 0.01 | < 0.01 | 0.01 | 63 |
| Leukemia | RPMI-8226 | < 0.01 | < 0.01 | < 0.01 | 50 |
| Leukemia | SR | < 0.01 | -- | 0.02 | 25 |
| Melanoma | LOX IMVI | < 0.01 | -- | 0.04 | 32 |

| | | | | | |
|---------------------|-----------|--------|--------|--------|-----|
| Melanoma | M14 | < 0.01 | < 0.01 | < 0.01 | 100 |
| Melanoma | MALME-3M | 0.01 | 0.01 | 0.05 | 100 |
| Melanoma | SK-MEL-2 | 0.06 | 0.02 | 0.51 | 100 |
| Melanoma | SK-MEL-28 | < 0.01 | 0.01 | < 0.01 | 50 |
| Melanoma | SK-MEL-5 | 0.06 | 0.10 | 0.08 | 40 |
| Melanoma | UACC-257 | < 0.01 | 0.02 | 0.02 | 79 |
| Melanoma | UACC-62 | 0.04 | 0.03 | 0.12 | 32 |
| Non-Small Cell Lung | A549/ATCC | < 0.01 | < 0.01 | < 0.01 | 50 |
| Non-Small Cell Lung | EKVX | -- | 0.05 | -- | 100 |
| Non-Small Cell Lung | HOP-62 | < 0.01 | 0.02 | < 0.01 | 32 |
| Non-Small Cell Lung | HOP-92 | 0.03 | -- | 0.13 | 50 |
| Non-Small Cell Lung | NCI-H226 | -- | 0.02 | -- | 50 |
| Non-Small Cell Lung | NCI-H23 | < 0.01 | 0.01 | 0.01 | 79 |
| Non-Small Cell Lung | NCI-H322M | < 0.01 | < 0.01 | < 0.01 | 63 |
| Non-Small Cell Lung | NCI-H460 | < 0.01 | 0.05 | 0.22 | 63 |
| Non-Small Cell Lung | NCI-H522 | < 0.01 | < 0.01 | < 0.01 | 40 |
| Ovarian | IGROV1 | < 0.01 | < 0.01 | 0.09 | 40 |
| Ovarian | OVCAR-3 | < 0.01 | 0.03 | 0.02 | 79 |
| Ovarian | OVCAR-4 | < 0.01 | 0.02 | < 0.01 | 100 |
| Ovarian | OVCAR-5 | 0.03 | < 0.01 | 0.04 | 40 |
| Ovarian | OVCAR-8 | < 0.01 | 0.02 | 0.02 | 63 |
| Ovarian | SK-OV-3 | 0.22 | 0.06 | 0.19 | 100 |
| Prostate | DU-145 | 0.02 | 0.06 | 0.13 | 40 |
| Prostate | PC-3 | < 0.01 | < 0.01 | 0.02 | 100 |
| Renal | 786-0 | < 0.01 | 0.04 | 0.03 | 63 |
| Renal | A498 | 0.03 | 0.03 | 0.03 | 32 |
| Renal | ACHN | 0.03 | 0.32 | 0.11 | 25 |
| Renal | CAKI-1 | -- | 0.79 | -- | 32 |
| Renal | RXF 393 | < 0.01 | < 0.01 | < 0.01 | 20 |
| Renal | SN12C | < 0.01 | < 0.01 | < 0.01 | 100 |
| Renal | TK-10 | < 0.01 | 0.07 | 0.05 | 63 |
| Renal | UO-31 | 0.01 | 0.17 | < 0.01 | 32 |

Although the invention has been described in detail for the purpose of illustration, it is understood that such detail is solely for that purpose, and variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention which is defined by the following claims.

WHAT IS CLAIMED:

1. A compound of the following formula:

**Formula I**

wherein:

- 10 R_1 are the same or different and independently selected from:

H;
 C_1 - C_4 -straight chain alkyl;
 C_3 - C_4 -branched chain alkyl;

- 15 $X =$ N;
 CH;

$R_2 =$ phenyl;

- 20 substituted phenyl, wherein the substituents (1-2 in number) are in any position and are independently selected from R_1 , OR_1 , SR_1 , $S(O)R_1$, $S(O_2)R_1$, NHR_1 , NO_2 , $OC(O)CH_3$, $NHC(O)CH_3$, F, Cl, Br, CF_3 , $C(O)R_1$, $C(O)NHR_1$, phenyl, $C(O)NHCHR_1CH_2OH$;

- 25 1-naphthyl;
 2-naphthyl;
 heterocycles including:

- 30 2-pyridyl;
 3-pyridyl;
 4-pyridyl;
 5-pyrimidyl;
 thiophene-2-yl;
 thiophene-3-yl;
 2-furanyl;
 3-furanyl;
 2-benzofuranyl;
 35 benzothiophene-2-yl;
 2-pyrrolyl;
 3-pyrrolyl;

- 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
 5 3-isoquinolinyl;
 4-isoquinolinyl;
 substituted heterocycle, wherein the substituents (1-2 in number) are in any position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;
- 10 R₃ are the same or different and independently selected from:
 H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 15 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined above in R₂;
- R₄= H;
 20 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
- R₃ and R₄ can be linked together by a carbon chain to form a 5-8-membered ring;
- 25 n= 0-3;
- Y= H;
 OR₁;
 NHR₁;
 30 NHC(O)R₃;
 NHISO₂R₃;
 NHC(O)NHR₃;
 NHC(O)R₅;
 NHC(O)OR₆;
- 35 R₅= C₃-C₇-cycloalkyl;
- R₆= C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 40 C₂-C₄-alkenyl chain;
 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined above in R₂; or a pharmaceutically acceptable salt thereof;
- 45 with the proviso that when R₁=CH(CH₃)₂, and R₂=Ph, and X=CH, then R₃≠H, and n≠0, and R₄≠H, and Y≠OH.

2. A compound according to claim 1, wherein X = N.

3. A compound according to claim 1, wherein

R₃ are the same or different and independently selected from:

- 5 H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

- Y= H;
10 OR₁;
NHR₁;
NHC(O)R₃;
NHSO₂R₃;
NHC(O)NHR₃; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein

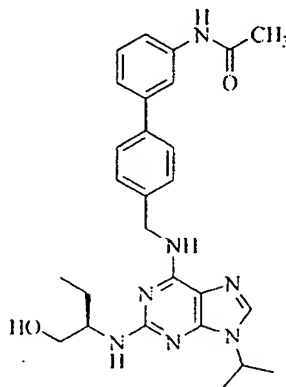
X= N;

R₃ are the same or different and independently selected from:

- 20 H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

- Y= H;
25 OR₁;
NHR₁;
NHC(O)R₃;
NHSO₂R₃;
NHC(O)NHR₃; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1, wherein the compound has the following formula:

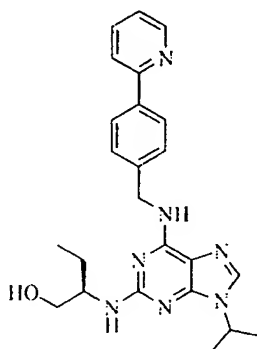


Formula VII

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1, wherein the compound has the following formula:

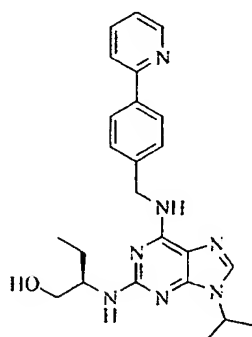
5



Formula XI

or a pharmaceutically acceptable salt thereof.

10 7. A compound according to claim 1, wherein the compound has the following formula:

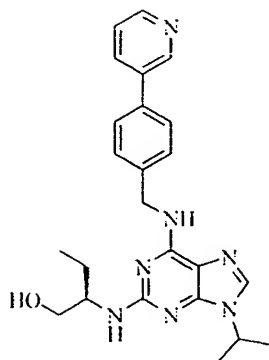


Formula XII

15 or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1, wherein the compound has the following formula:

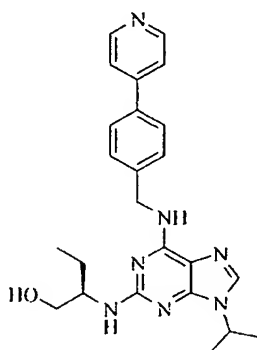
- 132 -



Formula XIII

or a pharmaceutically acceptable salt thereof.

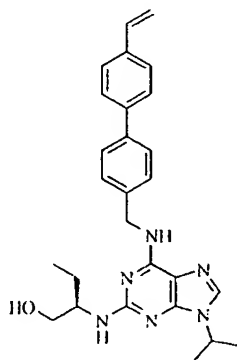
9. A compound according to claim 1, wherein the compound has the following formula:



Formula XIV

- or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1, wherein the compound has the following formula:

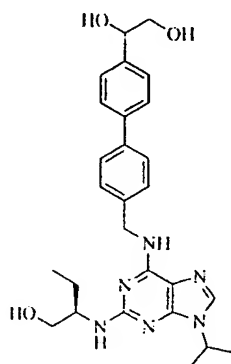


Formula XV

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1, wherein the compound has the following formula:

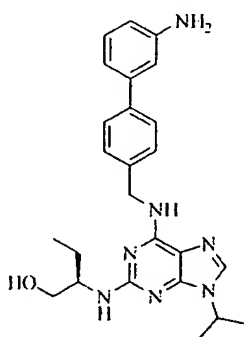
5



Formula XVI

or a pharmaceutically acceptable salt thereof.

10 12. A compound according to claim 1, wherein the compound has the following formula:

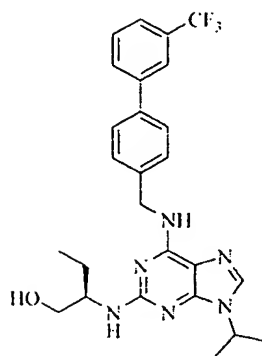


Formula XVII

15 or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 1, wherein the compound has the following formula:

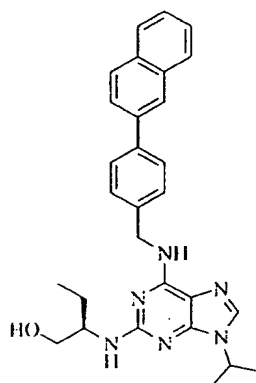
- 134 -



Formula XVIII

or a pharmaceutically acceptable salt thereof.

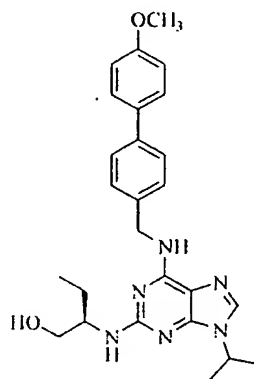
14. A compound according to claim 1, wherein the compound has the following formula:



Formula XIX

- or a pharmaceutically acceptable salt thereof.

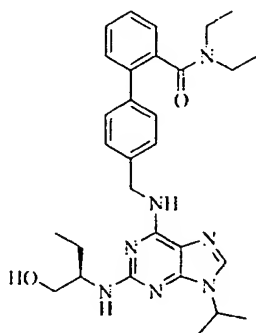
15. A compound according to claim 1, wherein the compound has the following formula:



Formula XX

or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1, wherein the compound has the following
5 formula:

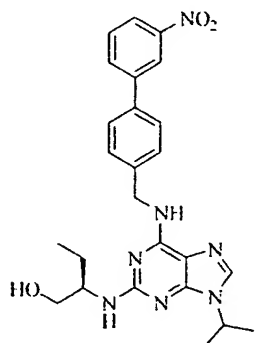


Formula XXI

or a pharmaceutically acceptable salt thereof.

10

17. A compound according to claim 1, wherein the compound has the following
formula:



Formula XXII

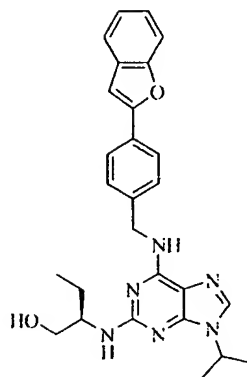
15

or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 1, wherein the compound has the following
20 formula:

20

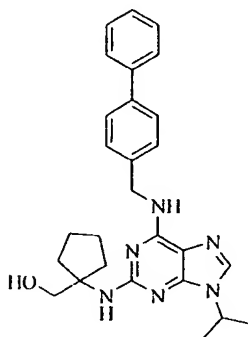
- 136 -



Formula XXIII

or a pharmaceutically acceptable salt thereof.

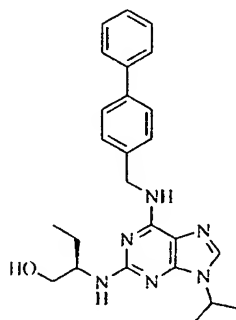
19. A compound according to claim 1, wherein the compound has the following formula:



Formula XXIV

- or a pharmaceutically acceptable salt thereof.

20. A compound according to claim 1, wherein the compound has the following formula:

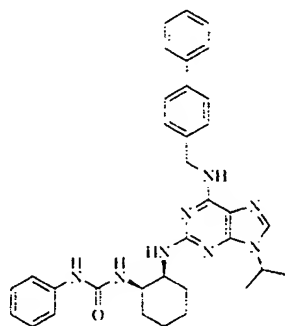


Formula XXVIII

or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 1, wherein the compound has the following formula:

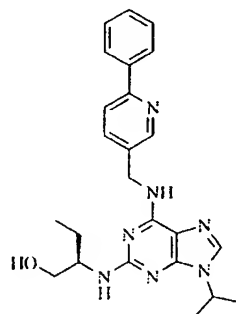
5



Formula XXXVI

or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 1, wherein the compound has the following formula:

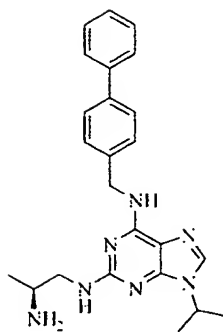


Formula XXXIX

or a pharmaceutically acceptable salt thereof.

23. A compound according to claim 1, wherein the compound has the following formula:

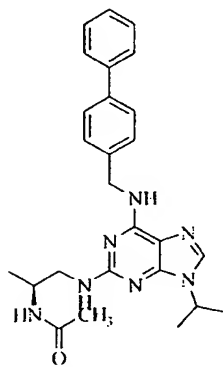
- 138 -



Formula I.H

or a pharmaceutically acceptable salt thereof.

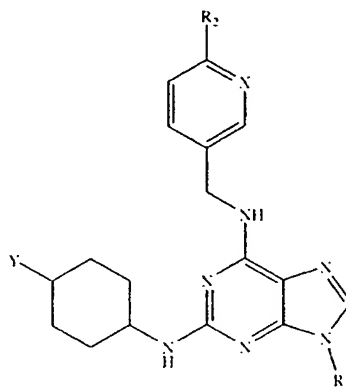
24. A compound according to claim 1, wherein the compound has the following formula:



Formula I.III

or a pharmaceutically acceptable salt thereof.

25. A compound of the following formula:



Formula III

15

wherein:

R₁ are the same or different and independently selected from:

H;
C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;

5

X= N;
CH:

R₂= phenyl;
substituted phenyl, wherein the substituents (1-2 in number) are in any
position and independently selected from R₁, OR₁, SR₁, S(O)R₁,
S(O₂)R₁, NHR₁, NO₂, OC(O)CH₃, NHC(O)CH₃, F, Cl, Br, CF₃, C(O)R₁,
C(O)NHR₁, phenyl, C(O)NHCHR₁CH₂OH;

heterocycles including:

15 2-pyridyl;
3-pyridyl;
4-pyridyl;
5-pyrimidyl;
thiophene-2-yl;
20 thiophene-3-yl;
2-furanyl;
3-furanyl;
2-benzofuranyl;
benzothiophene-2-yl;
25 2-pyrrolyl;
3-pyrrolyl;
2-quinolinyll;
3-quinolinyll;
4-quinolinyll;
30 1-isoquinolinyll;
3-isoquinolinyll;
4-isoquinolinyll;

substituted heterocycle, wherein the substituents (1-2 in number) are in any
position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

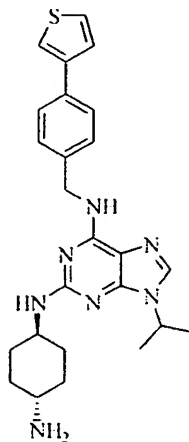
35

Y= OR₁;
NHR₁;
NHC(O)R₁;
NHSO₂R₁;
40 NHC(O)NHR₁;
NHC(O)OR₆; or a pharmaceutically acceptable salt thereof;

R₆ = C₁-C₄-straight chain alkyl;
C₃-C₄-branched chain alkyl;
45 C₂-C₄-alkenyl chain;
or a pharmaceutically acceptable salt thereof.

26. A compound according to claim 25, wherein X=N.

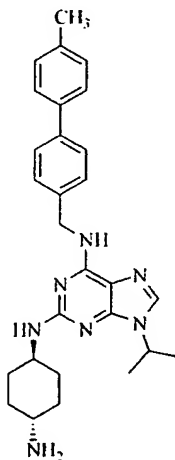
27. A compound according to claim 25, wherein the compound has the following formula:



Formula VIII

or a pharmaceutically acceptable salt thereof.

28. A compound according to claim 25, wherein the compound has the following formula:

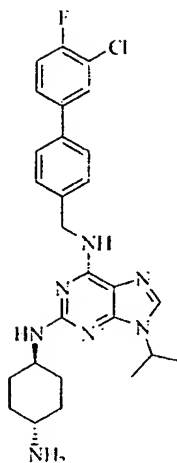


Formula IX

or a pharmaceutically acceptable salt thereof.

29. A compound according to claim 25, wherein the compound has the following formula:

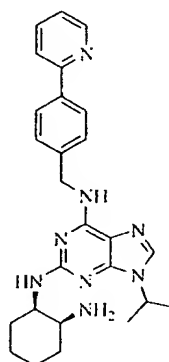
- 141 -



Formula X

or a pharmaceutically acceptable salt thereof.

- 5 30. A compound according to claim 25, wherein the compound has the following formula:

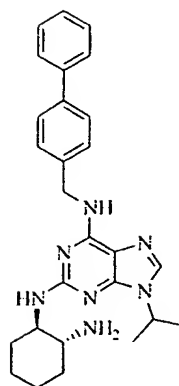


Formula XXV

- 10 or a pharmaceutically acceptable salt thereof.

31. A compound according to claim 25, wherein the compound has the following formula:

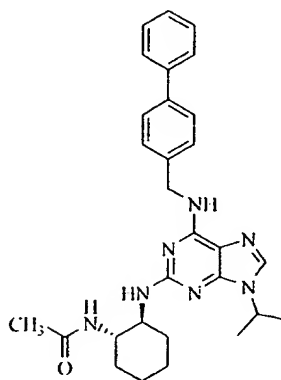
- 142 -



Formula XXVI

or a pharmaceutically acceptable salt thereof.

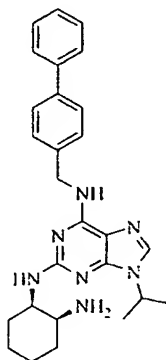
32. A compound according to claim 25, wherein the compound has the following formula:



Formula XXVII

- or a pharmaceutically acceptable salt thereof.

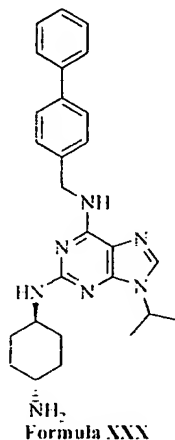
33. A compound according to claim 25, wherein the compound has the following formula:



Formula XXIX

or a pharmaceutically acceptable salt thereof.

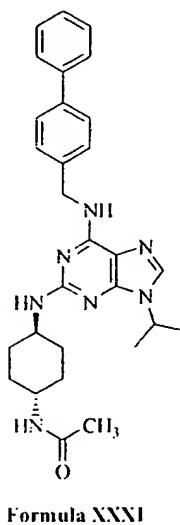
34. A compound according to claim 25, wherein the compound has the following
5 formula:



or a pharmaceutically acceptable salt thereof.

10

35. A compound according to claim 25, wherein the compound has the following
formula:



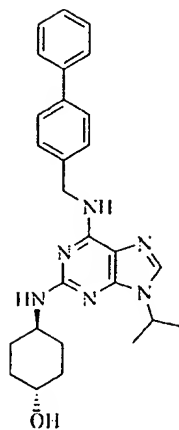
15

or a pharmaceutically acceptable salt thereof.

36. A compound according to claim 25, wherein the compound has the following
20 formula:

20

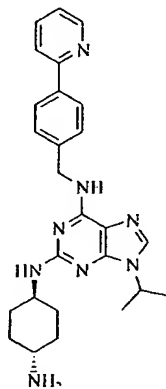
- 144 -



Formula XXXII

or a pharmaceutically acceptable salt thereof.

- 5 37. A compound according to claim 25, wherein the compound has the following formula:

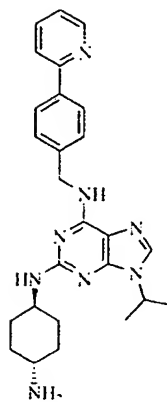


Formula XXXIII

- 10 or a pharmaceutically acceptable salt thereof.

38. A compound according to claim 25, wherein the compound has the following formula:

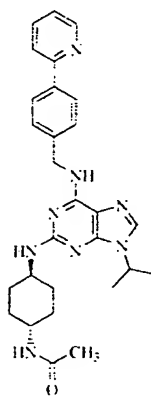
- 145 -



Formula XXXIV

or a pharmaceutically acceptable salt thereof.

- 5 39. A compound according to claim 25, wherein the compound has the following formula:

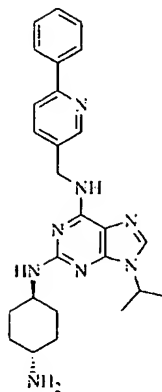


Formula XXXV

- 10 or a pharmaceutically acceptable salt thereof.

40. A compound according to claim 25, wherein the compound has the following formula:

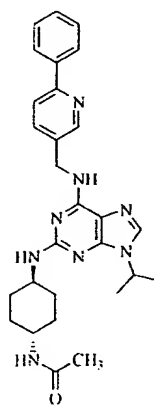
- 146 -



Formula XXXVII

or a pharmaceutically acceptable salt thereof.

- 5 41. A compound according to claim 25, wherein the compound has the following formula:

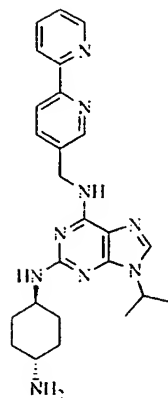


XXXVIII

- 10 or a pharmaceutically acceptable salt thereof.

42. A compound according to claim 25, wherein the compound has the following formula:

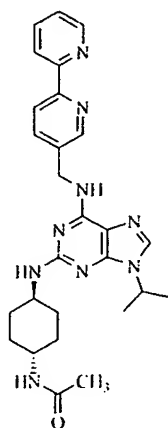
- 147 -



Formula XI.

or a pharmaceutically acceptable salt thereof.

- 5 43. A compound according to claim 25, wherein the compound has the following formula:

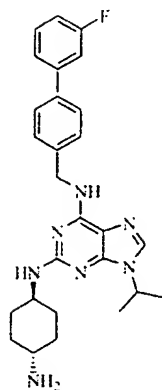


Formula XI.1

- 10 or a pharmaceutically acceptable salt thereof.

44. A compound according to claim 25, wherein the compound has the following formula:

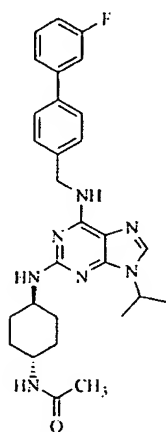
- 148 -



Formula XI.II

or a pharmaceutically acceptable salt thereof.

- 5 45. A compound according to claim 25, wherein the compound has the following formula:

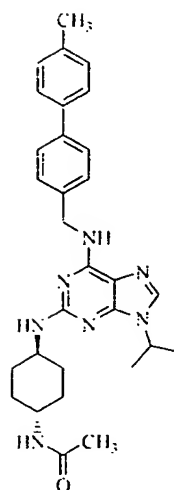


Formula XLIII

- 10 or a pharmaceutically acceptable salt thereof.

46. A compound according to claim 25, wherein the compound has the following formula:

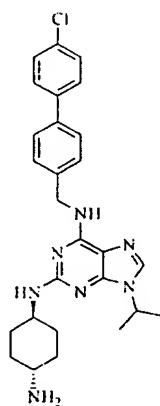
- 149 -



Formula XLIV

or a pharmaceutically acceptable salt thereof.

- 5 47. A compound according to claim 25, wherein the compound has the following formula:

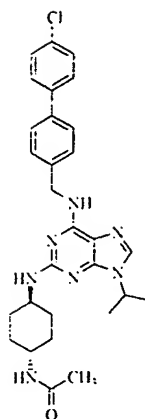


Formula XLV

- 10 or a pharmaceutically acceptable salt thereof.

48. A compound according to claim 25, wherein the compound has the following formula:

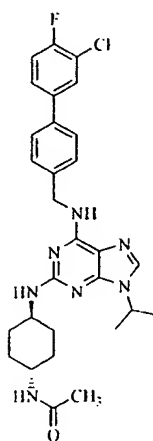
- 150 -



Formula XLVI

or a pharmaceutically acceptable salt thereof.

- 5 49. A compound according to claim 25, wherein the compound has the following formula:

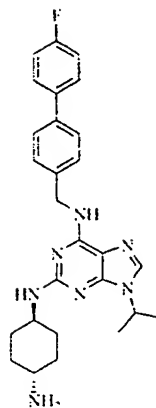


Formula XLVII

- 10 or a pharmaceutically acceptable salt thereof.

50. A compound according to claim 25, wherein the compound has the following formula:

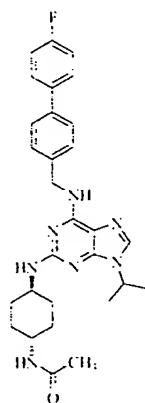
- 151 -



Formula XLVIII

or a pharmaceutically acceptable salt thereof.

- 5 51. A compound according to claim 25, wherein the compound has the following formula:

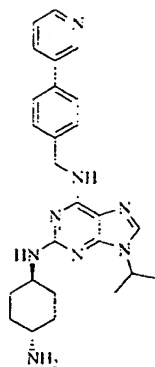


Formula II.

- 10 or a pharmaceutically acceptable salt thereof.

52. A compound according to claim 25, wherein the compound has the following formula:

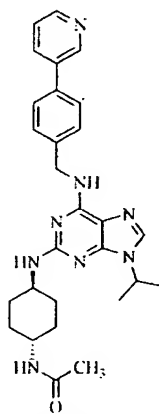
- 152 -



Formula I.

or a pharmaceutically acceptable salt thereof.

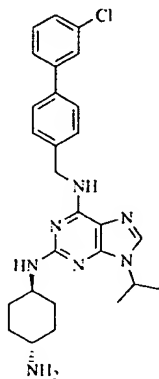
53. A compound according to claim 25, wherein the compound has the following formula:



Formula I.I

- or a pharmaceutically acceptable salt thereof.

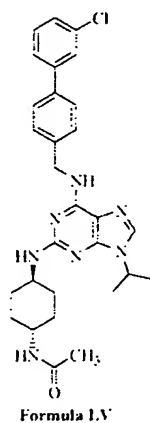
54. A compound according to claim 25, wherein the compound has the following formula:



Formula I.IV

or a pharmaceutically acceptable salt thereof.

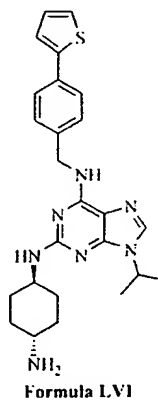
- 5 55. A compound according to claim 25, wherein the compound has the following formula:



or a pharmaceutically acceptable salt thereof.

10

56. A compound according to claim 25, wherein the compound has the following formula:



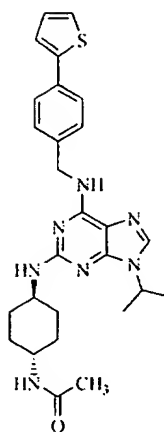
15

or a pharmaceutically acceptable salt thereof.

57. A compound according to claim 25, wherein the compound has the following formula:

20

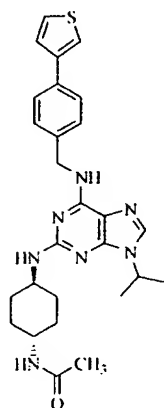
- 154 -



Formula LVII

or a pharmaceutically acceptable salt thereof.

- 5 58. A compound according to claim 25, wherein the compound has the following formula:

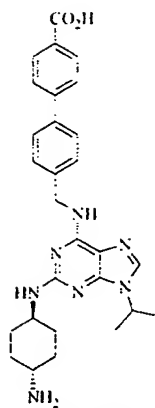


Formula LVIII

- 10 or a pharmaceutically acceptable salt thereof.

59. A compound according to claim 25, wherein the compound has the following formula:

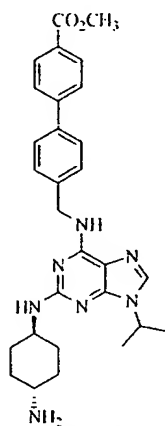
- 155 -



Formula LIX

or a pharmaceutically acceptable salt thereof.

- 5 60. A compound according to claim 25, wherein the compound has the following formula:

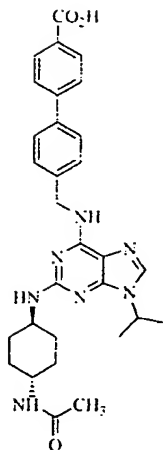


Formula LX

- 10 or a pharmaceutically acceptable salt thereof.

61. A compound according to claim 25, wherein the compound has the following formula:

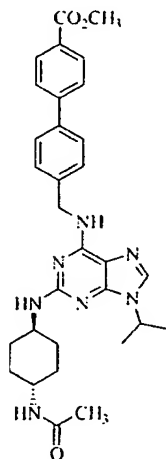
- 156 -



Formula LXI

or a pharmaceutically acceptable salt thereof.

- 5 62. A compound according to claim 25, wherein the compound has the following formula:

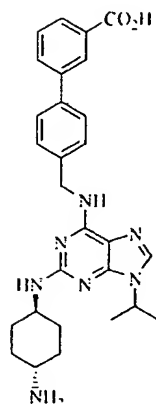


Formula LXII

- 10 or a pharmaceutically acceptable salt thereof.

63. A compound according to claim 25, wherein the compound has the following formula:

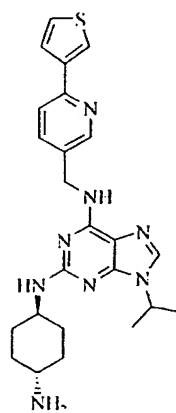
- 157 -



Formula LXIII

or a pharmaceutically acceptable salt thereof.

- 5 64. A compound according to claim 25, wherein the compound has the following formula:

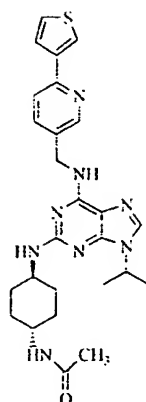


Formula LXIV

- 10 or a pharmaceutically acceptable salt thereof.

65. A compound according to claim 25, wherein the compound has the following formula:

- 158 -



Formula L.XV

or a pharmaceutically acceptable salt thereof.

5 66. A method for inhibiting cell proliferation in mammals comprising:
administering a therapeutically effective amount of the compound of claim 1
to the mammal.

67. The method of claim 66, wherein the compound is administered to a mammal
10 suffering from a cell proliferation disorder selected from the group consisting of
rheumatoid arthritis, lupus, type 1 diabetes, multiple sclerosis, cancer, restenosis,
gout, and other proliferative diseases involving abnormal cellular proliferation.

68. The method of claim 67, wherein the cellular proliferation disorder is cancer.

15

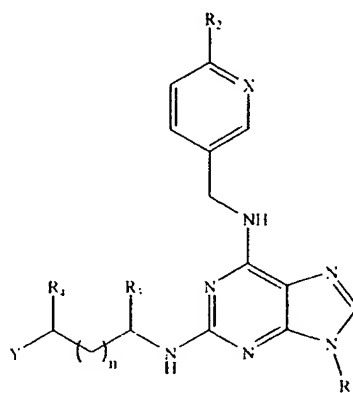
69. The method of claim 67, wherein the cellular proliferation disorder is
restenosis.

70. The method of claim 67, wherein the cellular proliferation disorder is type 1
20 diabetes.

71. The method of claim 67, wherein the mammal is human.

72. A pharmaceutical composition of matter comprising the compound of claim 1
25 and one or more pharmaceutical excipients.

73. A method for inhibiting cell proliferation in mammals comprising:
administering a therapeutically effective amount of the compound of claim 25
to the mammal.
- 5 74. The method of claim 73, wherein the compound is administered to a mammal
suffering from a cell proliferation disorder selected from the group consisting of
rheumatoid arthritis, lupus, type 1 diabetes, multiple sclerosis, cancer, restenosis,
gout, and other proliferative diseases involving abnormal cellular proliferation.
- 10 75. The method of claim 74, wherein the cellular proliferation disorder is cancer.
76. The method of claim 74, wherein the cellular proliferation disorder is
restenosis.
- 15 77. The method of claim 74, wherein the cellular proliferation disorder is type 1
diabetes.
78. The method of claim 73, wherein the mammal is human.
- 20 79. A pharmaceutical composition of matter comprising the compound of
claim 25 and one or more pharmaceutical excipients.
80. A process for preparation of a purine derivative compound of the formula:

**Formula X**

wherein:

R₁ are the same or different and independently selected from:

- 5 H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;

X= N;
 CH;

10

R₂= phenyl;
 substituted phenyl, wherein the substituents (1-2 in number) are in any
 position and are independently selected from R₁, OR₁, SR₁, S(O)R₁,
 S(O₂)R₁, NHR₁, NO₂, OC(O)CH₃, NHC(O)CH₃, F, Cl, Br, CF₃, C(O)R₁,
15 C(O)NHR₁, phenyl, C(O)NHCHR₁CH₂OH;

15

 1-naphthyl;
 2-naphthyl;
 heterocycles including:
20 2-pyridyl;
 3-pyridyl;
 4-pyridyl;
 5-pyrimidyl;
 thiophene-2-yl;
 thiophene-3-yl;
25 2-furanyl;
 3-furanyl;
 2-benzofuranyl;
 benzothiophene-2-yl;
 2-pyrrolyl;
30 3-pyrrolyl;
 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
35 3-isoquinolinyl;
 4-isoquinolinyl;

25

30

35

 substituted heterocycle, wherein the substituents (1-2 in number) are in any
 position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

40 R₃ are the same or different and independently selected from:

- H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
45 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
above in R₂;

$R_4 =$ H;
 C_1 - C_4 -straight chain alkyl;
 C_3 - C_4 -branched chain alkyl;

5 R_3 and R_4 can be linked together by a carbon chain to form a 5-8-membered ring:

$n =$ 0-3;

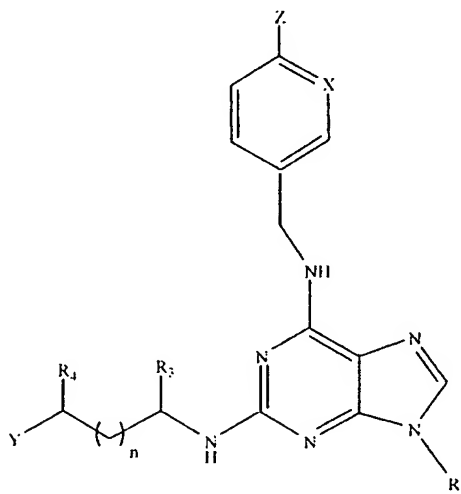
10 $Y =$ H;
 OR_1 ;
 NHR_1 ;
 $NHC(O)R_3$;
 $NHSO_2R_3$;
 $NHC(O)NHR_3$;
15 $NHC(O)R_5$;
 $NHC(O)OR_6$;

$R_5 =$ C_3 - C_7 -cycloalkyl;

20 $R_6 =$ C_1 - C_4 -straight chain alkyl;
 C_3 - C_4 -branched chain alkyl;
 C_2 - C_4 -alkenyl chain;
 $(CH_2)_nPh$;
 $(CH_2)_n$ -substituted phenyl, wherein the phenyl substituents are as defined
25 above in R_2 ; or a pharmaceutically acceptable salt thereof;

with the proviso that when $R_1 = CH(CH_3)_2$, and $R_2 = Ph$, and $X = CH$, then $R_3 \neq H$, and $n \neq 0$, and $R_4 \neq H$, and $Y \neq OH$, said process comprising:

30 reacting a first intermediate compound of the formula:



Formula IX

where

$Z = \text{Br or I}$

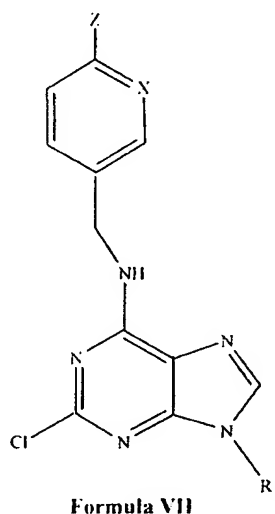
5

with a compound of the formula: $R_2\text{-B(OH)}_2$, $R_2\text{-Sn(n-Bu)}_3$, $R_2\text{-Sn(Me)}_3$, or mixtures thereof, under conditions effective to form the purine derivative compound.

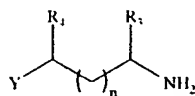
81. A process according to claim 80 further comprising:

10

reacting a second intermediate compound of the formula:



with a second compound of the formula:



15

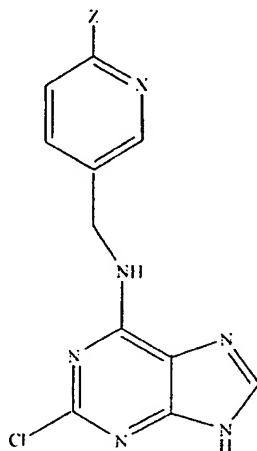
under conditions effective to form the first intermediate compound.

82. A process according to claim 81, wherein if Y in the second compound is

20 NH_2 , said process further comprises:

reacting the purine derivative compound with $R_3\text{C(O)Cl}$ or $R_3\text{SO}_2\text{Cl}$ or $R_3\text{NCO}$ or $R_3\text{OC(O)Cl}$ under conditions effective to form a final product having the same formula as the purine derivative compound except that Y is NHC(O)R_3 or NHSO_2R_3 or NHC(O)NHR_3 or NHC(O)OR_6 .

83. A process according to claim 81 further comprising:
reacting a third intermediate compound of the formula:

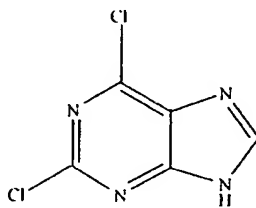


Formula VI

5

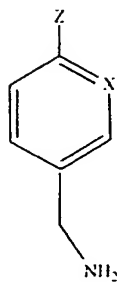
with a compound of the formula R₁-Z under conditions effective to form the second intermediate compound.

84. A process according to claim 83 further comprising:
10 reacting a first starting compound of the formula:



Formula IV

with a second starting compound of the formula

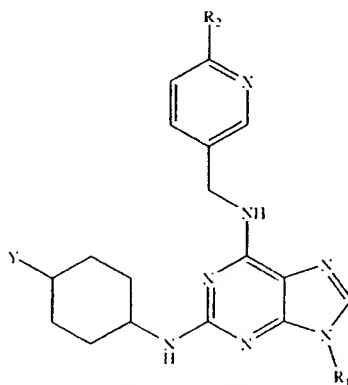


Formula V

under conditions effective to form the third intermediate compound.

5

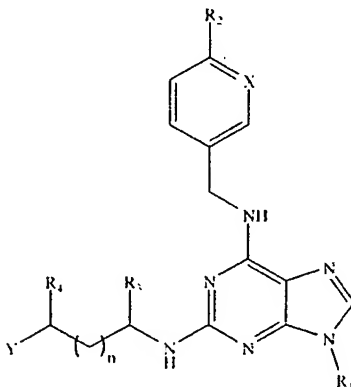
85. A process according to claim 80, wherein the purine derivative compound has the formula:



Formula III

10

86. A process for preparation of a purine derivative compound of the formula



wherein:

R₁ are the same or different and independently selected from:

- 5 H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;

X= N;
 CH;

10

R₂= phenyl;
 substituted phenyl, wherein the substituents (1-2 in number) are in any
 position and are independently selected from R₁, OR₁, SR₁, S(O)R₁,
 S(O₂)R₁, NHR₁, NO₂, OC(O)CH₃, NHC(O)CH₃, F, Cl, Br, CF₃, C(O)R₁,
 C(O)NHR₁, phenyl, C(O)NHCHR₁CH₂OH;

15

 1-naphthyl;
 2-naphthyl;
 heterocycles including:
 2-pyridyl;
 3-pyridyl;
 4-pyridyl;
 5-pyrimidyl;
 thiophene-2-yl;
 thiophene-3-yl;
 2-furanyl;
 3-furanyl;
 2-benzofuranyl;
 benzothiophene-2-yl;
 2-pyrrolyl;
 3-pyrrolyl;
 2-quinolinyl;
 3-quinolinyl;
 4-quinolinyl;
 1-isoquinolinyl;
 3-isoquinolinyl;
 4-isoquinolinyl;

20

25

30

35

 substituted heterocycle, wherein the substituents (1-2 in number) are in any
 position and are independently selected from Br, Cl, F, R₁, C(O)CH₃;

40 R₃ are the same or different and independently selected from:

- H;
 C₁-C₄-straight chain alkyl;
 C₃-C₄-branched chain alkyl;
 C₂-C₄-alkenyl chain;
 (CH₂)_nPh;
 (CH₂)_n-substituted phenyl, wherein the phenyl substituents are as defined
 above in R₂;

45

$R_4 =$ H;
 C_1 - C_4 -straight chain alkyl;
 C_3 - C_4 -branched chain alkyl;

5 R_3 and R_4 can be linked together by a carbon chain to form a 5-8-membered ring:

$n =$ 0-3:

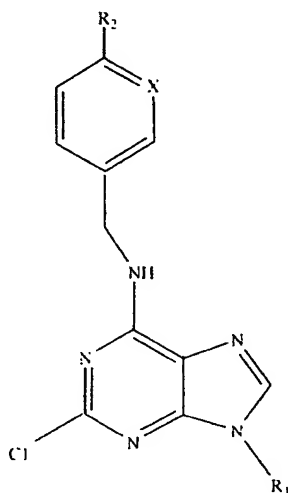
10 $Y =$ H;
 OR_1 ;
 NHR_1 ;
 $NHC(O)R_3$;
 $NHSO_2R_3$;
 $NHC(O)NHR_3$;
15 $NHC(O)R_5$;
 $NHC(O)OR_6$;

$R_5 =$ C_3 - C_7 -cycloalkyl;

20 $R_6 =$ C_1 - C_4 -straight chain alkyl;
 C_3 - C_4 -branched chain alkyl;
 C_2 - C_4 -alkenyl chain;
 $(CH_2)_nPh$;
 $(CH_2)_n$ -substituted phenyl, wherein the phenyl substituents are as defined
25 above in R_2 ; or a pharmaceutically acceptable salt thereof;

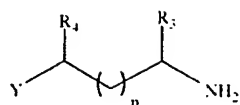
with the proviso that when $R_1 = CH(CH_3)_2$, and $R_2 = Ph$, and $X = CH$, then $R_3 \neq H$, and $n \neq 0$, and $R_4 \neq H$, and $Y \neq OH$, said process comprising:

30 reacting a first intermediate compound of the formula:



Formula XVII

with a compound of the formula:



Formula VIII

under conditions effective to form the purine derivative compound.

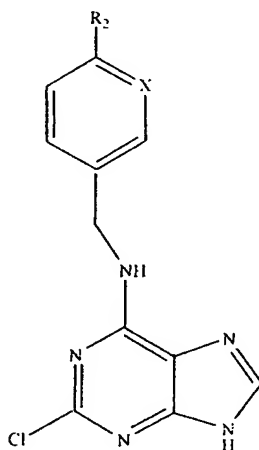
5

87. A process according to claim 86, wherein if Y in the second compound is NH_2 , said process further comprises:

reacting the purine derivative compound with $\text{R}_3\text{C}(\text{O})\text{Cl}$ or $\text{R}_3\text{SO}_2\text{Cl}$ or R_3NCO or $\text{R}_3\text{OC}(\text{O})\text{Cl}$ under conditions effective to form a final product having the same formula as the purine derivative compound except that Y is $\text{NHC}(\text{O})\text{R}_3$ or NHSO_2R_3 or $\text{NHC}(\text{O})\text{NHR}_3$ or $\text{NHC}(\text{O})\text{OR}_6$.

10

88. A process according to claim 86 further comprising:
reacting a third intermediate compound of the formula:

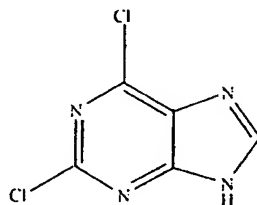


Formula XVI

15

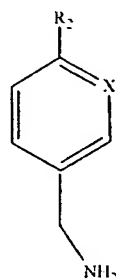
with a compound of the formula $\text{R}_1\text{-Z}$ under conditions effective to form the second intermediate compound.

89. A process according to claim 88 further comprising:
reacting a first starting compound of the formula:



Formula IV

- 5 with a second starting compound of the formula



Formula XV

- 10 under conditions effective to form the third intermediate compound.

INTERNATIONAL SEARCH REPORT

Int lional Application No

PCT/US 00/07065

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/16 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | SCHOW, S.R. ET. AL: "Synthesis and Activity of 2,6,9-Trisubstituted Purines" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 21, 1997, pages 2697-2702, XP002084930 cited in the application Table 1, compound 49 | 1-89 |
| X | WO 98 05335 A (THERAPEUTICS, INC.) 12 February 1998 (1998-02-12) cited in the application page 1, line 1 -page 3, line 20; claims; table 1 --- -/-- | 1-89 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

3 July 2000

Date of mailing of the international search report

19.07.00

Name and mailing address of the ISA

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Authorized officer

Helps, I

INTERNATIONAL SEARCH REPORT

In: tional Application No
PCT/US 00/07065

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Y | P. IMBACH ET. AL.: "2,6,9-Trisubstituted Purines. Optimisation Towards Highly Potent and Seletive CDK1 Inhibitors." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 9, no. 1, January 1999 (1999-01), pages 91-6, XP004154784 cited in the application table 1 ---- | 1-89 |
| Y | FR 2 741 881 A (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS.) 6 June 1997 (1997-06-06) page 1, line 1 -page 2, line 14; claims; examples ---- | 1-89 |
| Y | M. LEGRAVEREND ET. AL.: "Synthesis and In Vitro Evaluation of Novel 2,6,9-Trisubstituted Purines Acting as Cyclin-dependent Kinase Inhibitors" BIOORGANIC AND MEDICINAL CHEMISTRY, no. 7, 1999, pages 1281-93, XP000916148 table 1 ---- | 1-89 |
| P,Y | WO 99 43676 A (HOECHST MARION ROUSSEL) 2 September 1999 (1999-09-02) page 1, line 1 -page 20, line 13; claims; examples ----- | 1-89 |

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US 00/07065

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 66-71 and 73-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/07065

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